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This study investigated the use of a neuropsychological test battery to test human performance and evoked response decrements under the influence of a minor tranquilizer. A 10mg oral dose of diazepam (Valium) and placebo, preceded by baseline measurements, were administered on separate days resulting in four measurement sessions for each subject. A prototype neuropsychological test battery, capable of stimulus presentation, measurement, and storage was used to test (a) the steady state visual evoked response to both patterned and unpatterned multi-frequency stimulation; (b) the transient visual evoked response to both a stroboscopic flash and a transient stimulus imbedded in a tracking task; (c) critical flicker fusion (CFF); and (d) reaction time, error rate, and a cognitive positive peak (P300) evoked in response to tasks involving auditory discrimination, short term memory, and spatial processing. Means from two baselines and the placebo measurement session were combined and compared to the diazepam measurement session using paired t-tests. Physiological variables indicated significantly slowed neurological transmission speed (over)

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as well as deficits in visual acuity, attention, and intensity perception. The perception of both high frequency unpatterned flicker and CFF were unchanged. The perceptual evoked response also showed degradation accompanied by increased errors in the tracking task; however, amplitude did not degrade as the task became more difficult indicating neural activation as task involvement increased. The P300 showed latency increases and amplitude decreases accompanied by increased errors in the auditory discrimination task. Similar P300 decrements were noted in the short term memory task and the spatial processing task while the accuracy of the behavioral response remained largely unaffected. Additional analysis showed that the decrement was due largely to cognitive processing decrements caused by the diazepam. Power calculations showed that the significant differences were achieved with a high degree of confidence.

> Results indicated significant physiological, behavioral, and cognitive decrements in response to the diazepam. The simultaneous measurement of behavioral performance and cognitive evoked responses yielded an unprecedented ability to investigate the processing areas affected by the drug. Implications for more widespread use of the equipment and procedures are discussed.

side effects (drugs), performance, human, (KT)

PREFACE

The purpose of this study was to test the effects of a 10 mg oral dose of diazepam (valium) on psychophysiological and performance measures. The neuropsychological Workload Test Battery was used to monitor the effects. The research effort was performed in support of Project 7184 by the Armstrong Aerospace Medical Research Laboratory (AAMRL), Human Engineering Division, Wright-Patterson Air Force Base, Ohio 45433-6573.

The study is partial fulfillment of the requirements for a doctoral degree from Bowling Green State University, Bowling Green, Ohio under Air Force Institute of Technology sponsorship.

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Sincere gratitude is also expressed to the author's family whose encouragement and understanding served as constant inspiration toward the accomplishment of this educational goal.

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INTRODUCTION

Both the transient and steady state evoked responses have found considerable utility in research involving neuropsychological, behavioral, cognitive, and clinical assessment (Beck, 1975; Chiappa & Ropper, 1982; Davies & Parasuramen, 1977; Donchin, 1968; Donchin & Cohen, 1967, 1969; Donchin & Sutton, 1970; Kutas, McCarthy, & Donchin, 1977; Regan, 1975, 1977a, 1977b; Shaefer, 1977). Several separate lines of research over the past decade have focused on discrete aspects of the human evoked response in an effort to demonstrate its validity and reliability as a diagnostic tool. For example, the visual evoked response has been studied extensively in terms of its ability to assess visual acuity. Harter and White (1970) were among the first to note that there were systematic changes in the transient visual evoked response to a patterned stimulus with progressive defocussing. These authors, using a checkerboard pattern flashed at the rate of once per second (1 Hz) found that the subjects' averaged electroencephalographic (EEG) response contained peaks that were maximal when the image was in focus. These authors suggested that the spherical correction for an unknown eye could be determined by systematically inserting corrective lenses until an optimal evoked response was obtained. Since further study demonstrated this measure to be a sensitive and objective index of acuity (Marg, Freeman, Peltzman, & Goldstein, 1976), correlating with more tediously determined psychophysical thresholds, its impact in clinical diagnostics has been considerable.

Increased applicability of this technique was obtained by Regan (1977a) who flashed the checkerboard at a faster rate (7-15 Hz) and

obtained a sinewave (Steady State) output from the brain whose averaged amplitude was an equally good index of visual acuity. The amount of time required to obtain the response in this manner was thus drastically reduced. Further refinements of the technique (Regan, 1977b) resulted in the ability to generate this measure without intruding with an ongoing visual task. It is this nonobtrusiveness, along with its precision, that makes the evoked response an attractive technique for human engineering, medical, and educational applications since data can be collected while not interfering with the subjects' primary performance (e.g. Donchin, 1977; Prichard, 1981).

Use of the evoked response (both transient and steady state) is by no means limited to visual acuity. Both the absolute latency and the difference in latency between the two eyes tested monocularly are sensitive indicators of visual pathway functioning. A recent review by Chiappa and Ropper (1982) discusses the use of these measures as indicators of such diseases as optic neuritis, multiple sclerosis, glaucoma, Parkinson's disease, amblyopia, and lesions and tumor compression of the anterior visual pathways.

An evoked response can also be generated to auditory stimulation. Several studies (Davies, 1976; Hecox & Galambos, 1974; Jewett & Williston, 1971) have described a click evoked response recorded from the human scalp in the first 10 milliseconds (msec) after stimulation. The normal response can be divided into distinct peaks that originate in specific midbrain and peripheral structures along the auditory pathway. Further, this response is independent of the cortical state of the subject. Thus, testing can be

accomplished with the subject awake, asleep, sedated, or while he is attending to another task--enhancing its usefulness as a nonobtrusive measure of auditory function.

The transient evoked response has also proved to be an extremely durable measure of cognitive relevance. After it was recognized that the evoked responses to relevant stimuli were larger than those to nonrelevant stimuli (Chapman, 1965), several investigations set about establishing the parameters of the response which measured such relevance (Beck, 1975; Donchin et al., 1967, 1969, 1970). It became clear that the major characteristic of the evoked response sensitive to cognitive function is the large positive peak which occurs between 200 and 500 msec after a discrete stimulus. This peak is absent if decision or attention is not required from the subject and, when it occurs, seems to be capable of indexing a wide variety of stimulus meaning and relevance. Beck (1975) reviewed the literature dealing with this positive component (called P3 or P300) and concluded that it is enhanced when and only when cognitive information is being actively processed. Further study of the amplitude and latency measures of the P300 and its associated peaks (both pre and post) have identified characteristic changes that occur in its morphology due to memory load, fatigue, reaction time, and information processing time (Chapman, 1973; Donchin & Lindsley, 1966; Gomer, Spicuzza, & O'Donnell, 1976; Squires, Wickens, Squires, & Donchin, 1976).

Specific research has also recently been directed toward using the evoked potential in the assessment of applied behavioral and job-related performance capabilities. For example, several investigators have used the

evoked response to assess residual attention while the workload or difficulty of a visual task was increased (Wickens, Israel, & Donchin, 1976; Wickens, Israel, McCarthy, Gopher, & Donchin, 1977). These investigators presented an auditory task to their subjects during the course of a manual tracking task. The secondary auditory task consisted simply of counting the tones of a specific frequency.

Two frequency levels were used (high and low), and the counted tones were presented less frequently than the tones not to be counted. The evoked response was measured from the onset of each tone. Results demonstrated a dramatic reduction in the evoked response amplitude of the counted tones with the imposition of the tracking task. Analysis based on the difficulty of the tracking task and the sequential dependency of the evoked response to the tone presentations provided a graded measure of subject loading. These results are most intriguing since they suggest that an unobtrusive, secondary auditory task is able to index the visual workload of a subject, and do so in a graded way.

Donchin and his colleagues (Israel, Wickens, Chesney, & Donchin, 1980) took this discovery a step further and simulated an air traffic control task composed of monitoring symbolic representations of aircraft moving in straight line paths across a display screen. The subjects were required to manually respond to sudden changes in the displayed trajectories of certain aircraft. Mental workload was manipulated by varying the number of aircraft to be monitored simultaneously. Again, auditory probes were presented to the subjects as a series of low and high pitched tones. The subjects were instructed to count the infrequent, high-pitched tones and to

report the count at the end of each trial. It was found that certain components of the evoked potential measured in response to the high tone showed a monotonic reduction in area as the number of displayed aircraft was increased from zero to eight.

Natani and Gomer (1981) in an attempt to take this technology out of the laboratory and into a situation in which subjects performed operationally relevant tasks, used the above technique during flight simulation at a McDonnell Douglas Astronautics research facility. These authors employed concurrent pilot tasks including following a prespecified flight profile (through pitch and bank angle adjustments) while maintaining constant airspeed; monitoring for auditory threat warnings, with switch activation required for threat avoidance; and tracking, acquiring, and designating a symbolic target on a monitor display. The simulation took the form of an attack aircraft flying an air to ground strike. Workload was manipulated by simulating wind gust disturbances which varied the difficulty of following the pitch and bank angle demands required to maintain level flight. The high and low pitched tones were the auditory threat warnings generated in the pilot's headphones. The low frequency tone indicated a missile launch that required a pilot-initiated countermeasure. Again, tne results showed a reliable decrease in evoked response area as well as an increase in latency as the workload level increased.

In a related series of studies, Lewis (1983) and Lewis and Rimland, (1980) attempted to test the potential use of evoked response measures in predicting, or improving the prediction of, the performance of sonar operators and other Navy personnel required to make quick decisions and to

possess high levels of spatial ability. For example, in an attempt to use the evoked response to predict aviator performance, these authors generated a series of hemispheric asymmetry studies aimed at differentiating pilots from radar intercept officers. It was felt that pilots represented a group of individuals who required superior spatial skills, while the radar intercept operators required more analytic abilities. Since verbal or analytic information is usually associated with left hemisphere activity, and spatial or integrative processing with right hemisphere activity, it was hypothesized that the evoked response measured simultaneously from both hemispheres should show an asymmetry in favor of the dominant hemisphere. Substantial evoked response differences were found between the two groups and ongoing research is focussing on using this asymmetry as a predictor of successful performance in these types of jobs.

Finally, a recent development in this area is a behaviorial assessment battery called the Criterion Task Set (CTS) developed by Shingledecker (1984) and designed specifically for applied human performance assessment. This is a battery that can be presented on a single monitor with user-friendly software. The tasks chosen for this battery are firmly based in current theoretical models of perceptual-motor and cognitive behavior. It has the added refinement of delineating (by task) three primary stages of processing dedicated to perceptual input, central processing, and response behavior. Within each of these stages are resources associated with the mode of input (visual/auditory), the code in which the central processing is performed (spatial imaginal/abstract symbolic), and the mode of response output (manual/vocal). Further, this battery divides central processing to differentiate between working memory and the specific types of processing

or decision functions that occur at this stage. The battery is also capable of presenting each task at three distinct difficulty levels. Although developed primarily as a behavioral rather than a neurophysiological battery, several of the tasks (manual response time, spatial processing, tracking, etc.) are appropriate for concurrent evoked response measurement.

The discovery of the evoked potential and the research described above has done much in terms of providing an objectively measurable indicator of several aspects of human performance and condition. However, the range of equipment required to carry out this type of research is staggering both in numbers and in expense. The computers, stimulus equipment, calibrators, filters, amplifiers, recording devices and analysis devices typically fill an entire laboratory and can be configured to study only one type or aspect of the evoked response at a time. To change, say, from studying the evoked response to patterned stimuli to an experiment designed to analyze the P300 response to a memory task requires disconnecting equipment, introducing new stimulus devices, recalibrating filters and amplifiers, changing software, and connecting a completely different analysis device. The study of this important human response would be enhanced indeed if it were possible to construct a single device which incorporated stimulus generation, storage, and analysis capabilities. Inter-laboratory standardization of measurement would also be an important consequence of such a device. Access to the prototype of such a device was provided by the Air Force for the purpose of this study. The individual tests that were chosen for this study were incorporated into the software of the device (hereafter referred to as the test battery) and thus provided all the advantages of several separate

pieces of stimulus and analysis equipment currently found in clinical and laboratory settings.

Once adequate reliability and validity were established by field testing, the battery could be hard wired and, by means of extensive interpretation guides, administered, analyzed, and interpreted by technicians, hospital staff, and trained laboratory personnel without extensive professional assistance. The microminiaturization of such a battery would allow its incorporation into human operated machine design to detect operator fatigue, perceptual distortion, and performance degradation. A simple feedback loop could be incorporated in the equipment to provide warning once amplitudes and latencies exceeded a pre-set limit. The combination of cognitive, perceptual and behavorial tasks would enable the battery to be used in educational or assessment facilities. Software incorporation of other measures specific to learning ability or specific capabilities desired in a work environment would allow the battery to be used in learning disability assessment and in job selection where potential workload is high. The military has obvious interest in such a device as a means to imbed performance assessment capabilities into human operated weapons systems. Interest has also been expressed by NASA which could incorporate such a device in space environments where optimum human performance is essential in man/machine interaction. The sensitivity of the proposed measures to neurological damage, demyelination, and visual and auditory pathway lesions would have implications in terms of the clinical assessment of neurological integrity and diagnosis. In experimental or human engineering settings, it is possible to conceive of the battery being

used as a standardized measure of fatigue, psychological distress, and attention in both basic and applied settings.

In line with these proposed uses, the battery must be able to measure visual, auditory, behavioral, cognitive, and physiological performance either singly or simultaneously in a variety of settings. The problem that arises at this point is how to calibrate the battery, i.e., to develop a standard against which to gauge the potential performance decrement in question. Most logically, use of an agent with known decremental effects on the measures would be an appropriate first step. Measurement of a known drug effect would serve the purposes of testing the battery's sensitivity to a fixed dosage level and calibrating the battery to use the measured effect as a standard against which to later gauge the effects of a variety of chemical agents or conditions that produce similar decrements.

Several evoked response measures have been shown to exhibit considerable psychophysiological sensitivity to the benzodiazepines. Chlordiazepoxide, nitrazepam, oxazepam, and diazepam have generally been found to impair psychomotor skills, depress critical flicker fusion and auditory flutter fusion thresholds, increase the latency and decrease the amplitude of both somatosensory and visual evoked potentials, and decrease subjective mood levels and attentiveness (Kleinknecht & Donaldson, 1975; Shagass, 1974; Shagass & Straumanis, 1978; Sherwin, 1971). The drug that produces the most consistent effects on these measures is diazepam (Valium). The relative absence of adverse side effects with clinical doses (.50-10 milligrams [mg] intravenously and 5-20 mg orally), less drowsiness, low overdose potential, and high tolerance made diazepam an ideal drug for this study.

Learning and memory tasks have also been used to study the decremental effects of diazepam exposure and have resulted in the conclusion that diazepam impairs the retention of new information rather than the retrieval of previously learned material (Clarke, Eccersely, Frisby, & Thornton, 1970; Haffner et al., 1973; Liljequist, Linnoila, & Mattila, 1978). Finally, increased workload and diazepam induce similar decrements in the amplitude and increases in the latency of various components on the evoked response. These, combined with an increased error rate and longer reaction times, have been found to correspond to decrements in attention, psychomotor skills, perception, vigilance, and cognitive performance capabilities (Donchin, 1977; Rizzuto & O'Donnell, 1981; Seppala, Pavla, Matilla, Kortilla, & Shrotriya, 1980; Wickens, Israel, & Donchin, 1977; Wilson & O'Donnell, 1980).

Accordingly, a pilot study was completed (Rizzuto, Wilson, Palmer, & Yates, 1984) that employed a single 5 mg oral dose of diazepam and placebo in a double-blind, repeated measures design and measured pre- and post-ingestion effects on a wide range of evoked response and clinical measures sensitive to diazepam induced performance decrements. These measures included the steady state evoked response to both patterned and unpatterned stimuli, a short term memory task, grip strength and electromyographic measures, an auditory evoked response, a transient visual evoked response, and a critical flicker fusion threshold measurement. The 5mg dose was employed as a conservative dosage level that would allow the observation of any potential untoward effects of tranquilizer ingestion in an essentially diazepam-naive group of subjects.

The results of the pilot study indicated no generalized significant effect on any of the visual, auditory, memory, behavioral, or physiological variables studies. Self reports of subjective, postingestion effects indicated that the majority of subjects felt no different after either diazepam or placebo ingestion. Two subjects reported feeling slightly more relaxed after the diazepam ingestion but could not differentiate as to whether the feeling was caused by the drug or by the fact that they had been sitting comfortably for half an hour. Their performance, in either case, was not different from the performance of subjects who reportedly felt no different from the way they had before drug ingestion.

Given that the majority of studies in the literature used 10-20mg of oral diazepam before achieving significant effects, these were not surprising results. One review article (Kleinknecht & Donaldson, 1975) showed that out of 24 studies reviewed that measured cognitive or psychomotor performance, 21 used a 10-20mg dosage with significant effects centering primarily in the 15-20mg range.

Since, in the current experiment, we intended to measure several of the same types of variables presented in the literature (memory, coordination, vision, reaction time, etc.) it was considered desirable to use a diazepam dosage designed to yield consistent and replicable effects. Given that the literature reviewed indicated that some of the proposed subtests may be more sensitive to drug effects than others and that the lower dosage levels yielded inconsistent or nonsignificant results, the use of a higher dosage level seemed appropriate. The present experiment, therefore, was designed around a 10mg oral dose of diazepam in an attempt to increase the

measurable effect size using essentially the same paradigm as the pilot study. The 10mg dose is well supported in the literature and is within normal clinical dosage range (Physician's Desk Reference, 1985). It was anticipated that the sensitivity of these measures would result in measurable differences from baseline levels that were not previously detected by the majority of the methods reported in the literature.

In addition to the increase in dosage level, the current study was modified by dropping the grip strength and electromyographic measures used in the pilot study and adding two tasks from Shingledecker's (1984) CTS behavioral battery. This was done for several reasons. First, the grip strength data (generated by a hand-held dynamometer) was by far the least objective as well as the least automated measure in the pilot study. Data collection required the experimenters to gauge the displacement of a meter while the subject squeezed the dynamometer, and subjectively decide when the displacement was at maximum. Second, the electromyographic data collected concurrently with the squeeze was completely lost due to an equipment design flaw. Although the malfunction was correctable, the two CTS tasks (described in detail in the methods section) offer fully automated data collection and more potential information and sensitivity in pinpointing where potential input, processing, or output decrements are occurring in response to the drug. More importantly, the two CTS tasks chosen (spatial processing and unstable tracking) offer an opportunity to increase the ecological validity of the prototype battery by testing the human resources required for the processing or production of spatial information, manipulation, manual response, and speed and accuracy. These, in turn, are related to the behaviors of maintaining orientation, pattern

identification, position analysis, manual control, error correction, and control actuation. Finally, the unique capability of the simultaneous measurement of visual and cognitive evoked responses during CTS task performance was added to the battery to offer neurophysiological evidence of behavioral performance decrements due to the drug as well as decrements due to the workload level.

The aim of the current study was to use the revised test battery to: (1) ascertain its measurement of overall performance effects during human exposure to an increased (10mg) oral dose of diazepam and placebo, (2) to gauge which of the subtests, if any, are differentially sensitive to diazepam at this dosage level, (3) to increase the sensitivity and ecological validity of the battery by adding behavioral tasks designed to measure spatial processing and tracking abilities, and (4) upon finding these answers, to calibrate and refine the battery for use in further research and validation.

METHOD

Subjects

Air Force active duty male volunteers were solicited through basewide advertisement in a weekly bulletin at Wright-Patterson Air Force Base, Ohio. Potential subjects were administered the Cornell Medical Index (Weider, Wolff, Brodman, Mittelmann, & Wechsler, 1949) to screen psychosomatic and neuropsychiatric disturbance. A stringent cutoff level was established allowing rejection of any subject scoring 7 out of 101 possible affirmative answers. This cutoff allowed rejection of approximately 90% of all testees with indications of a neuropsychiatric or psychosomatic disorder. The potential subjects were next interviewed by the experimenter who ascertained family and individual psychiatric and medical history, past and current medication use, allergies to any drugs, previous diazepam experience, seizure history, visual and auditory difficulties, alcohol use, glaucoma history, depression, suicidal tendencies, and a subjective evaluation of the individual's emotional stability. Finally, the volunteers were given a brief medical examination by an Air Force physician who also made a final evaluation regarding any medical or psychiatric history that was in question. Surprisingly, none of the volunteers was rejected by the Cornell Index or any of the other criteria. Attrition was due solely to schedule and work conflicts.

In this manner, 28 male subjects were selected for the experiment. Each was given both an oral and a written explanation of the study, provided the opportunity to ask questions, and asked to sign a consent form.

Subjects were told that the study was to evaluate the effects of various substances on several performance measures, and that one of the substances of interest that they may have heard about previously was valium.

Procedure

Prior to their actual day of service, subjects were introduced to the laboratory, seated inside the sound and light proof test chamber, and given exposure to each test condition on which they were to be measured. The tests were presented in the same order as they were to be presented during the experiment and consisted of the steady state evoked response to an unpatterned stimulus, a short term memory task designed by Sternberg (1969), a spatial processing task (CTS), a tracking task (CTS), an auditory discrimination task, the steady state evoked response to a patterned checkerboard stimulus, the transient evoked response to a strobe light, and a critical flicker fusion threshold measurement. Each of these is described in more detail below. This procedure gave each subject the opportunity to familiarize himself with the modes of stimulus presentation and to practice those tasks requiring subject response. Subsequent practice (approximately 2 hours) was given on the two CTS tasks to ensure asymptotic performance. Subjects were then scheduled for two service days separated by a 48 hour inter-session interval (to allow the ingested diazepam to pass from the system between actual measurement days). Subjects were cautioned not to ingest any alcohol or medication for 12 hours before and after each measurement session. They were also advised to get a normal night's sleep prior to the day of their participation and to eat a light breakfast

beforehand. Each was asked to verify these conditions on the days of service.

The study employed a double blind, two session (diazepam and placebo) repeated measures design with each subject acting as his own control. Thus, on his first day of participation, each subject was first tested on each of the measures to establish baseline levels. After completion, the experimenter administered and observed ingestion of one of two possible unmarked capsules taken from separately numbered bottles. One bottle contained 10mg capsules of diazepam, and the other an identical capsule containing the placebo. The balanced design resulted in 14 randomly assigned subjects receiving a capsule from bottle number 1 on their first day of service and 14 subjects receiving a capsule from bottle number 2 on their first day. Since the peak effect of the diazepam was expected approximately one hour after ingestion (Physician's Desk Reference, 1985), and subject measurement time took approximately 60 minutes, the retests did not begin until 30 minutes after ingestion. This resulted in peak drug effect occurring during the middle of each measurement session. The retests were administered in the same order as the baseline sequence to obtain approximately equal test/retest time intervals. At the completion of the retest session, subjects were again checked by the physician if necessary to assess any persistent symptoms. The pharmokinetics of diazepam are such that any significant effects were absent by the end of the duty day. The medical monitor remained on site until the peak drug effect had passed. In contrast with the previous experiment using 5mg where all subjects were allowed to return to their duty stations, subjects in this experiment were transported to their place of residence and not allowed to

drive or return to their duty station until the next day. Attempts were also made to have someone on the premises to monitor the subject should any symptoms develop or persist. The phone numbers of the experimenter and the medical monitor were provided to each subject. Three subjects were run each morning between 8 a.m. and 12 noon to ensure that any possible drug effects would be gone by the end of the duty day, and to control for circadian effects. Two mornings later, the subjects arrived in the same order and the same test/retest procedure was followed. The only difference was that each subject was administered the capsule he had not received on his first day of service.

Equipment-Testing Sequence

During measurement sessions, electroencephalograms were recorded on magnetic tape from both the occipital (OZ) and parietal (PZ) lobes via Beckman silver/silver chloride electrodes attached to the scalp with adhesive collars and grounded to the mastoids according to the international 10-20 electrode placement system (Jasper, 1958). Resistance between the electrodes was less than 5 Kohms. Electrooculograms were recorded in the same manner from an electrode placed above the right eyebrow. All electrical data from the skull was amplified and filtered through standard Grass P511 AC amplifiers with an effective bandpass of .1 to 300 Hz before recording. All subjects were visible to the experimenters by means of a TV camera trained on the subject's face and connected to an external monitor outside the subject booth. Leads from the skull were attached to a patch box which fed subjects' data to all measurement equipment outside the subject booth. All stimuli were visible through a glass window in the wall of

the subject booth approximately 80 cm from where the subjects were seated. The prototype battery whose software was used to control stimulus presentation and ultimately averaged and analyzed most of the subjects' data consists of an LSI 11/23 microprocessor utilizing 16 channels of amplified physiological and psychophysiological data. The sequence of tests during each of the four measurement sessions (Baseline 1, Day 1 Post-Ingestion, Baseline 2, Day 2 Post-Ingestion) and the apparatus specific to the individual tasks was as follows:

Steady state evoked response to unpatterned stimuli. The steady state evoked response to unpatterned stimuli was elicited by two small horizontal flickering fluorescent tubes 23.5cm long and 12.1cm apart. The subject was told to fixate on a black dot between the tubes on a white background and not to blink during the test. The tubes were sinusoidally modulated at three separate frequency classes (low, medium, high) each consisting of the sum of three separate frequencies within the class (8, 9, and 12Hz for low; 14, 17, and 20Hz for medium; and 42, 46, and 50Hz for high). The space averaged luminance was approximately 50 foot-lamberts. Data from this test was acquired from two analog-to-digital channels (EEG and stimulus) where the stimulus channel was input from the light source as measured by a photodetector and EEG was recorded from the occiput. The measurement of stimulus and EEG data, averaged over 20, two second epochs for each stimulus class, was carried out by the test battery and stored on a temporary disc for later analysis. Data collection time was approximately 3 minutes. This measure was designed to yield information about the subject's visual perception and neural transmission speed in the visual cortex.

Auditory discrimination task. The subject was next handed a pair of lightweight earphones and told that he would be presented with a series of short tones - some low (1200Hz) and some high (1400 Hz). He was also told that the high tones would occur less frequently than the low tones (about 80:20) and that the task was to count the high tones. After the subject was seated back comfortably with eyes closed (to control for eye movements and blinks) and earphones in place, the task was begun. The test battery presented approximately 100 tones at two second intervals. Tone epoch length was 100ms and the proportion of high to low was random at about 20-25% high. In addition, the test battery generated a trigger pulse 150ms prior to the onset of each tone and recorded the brain's response (auditory evoked potential) from that point to 850ms after tone presentation. Responses to both high and low tones were stored separately for future analysis. At the conclusion of the task, the subject was asked to report the number of high tones counted, and the number was recorded for later comparison with the number of high tones the battery had generated.

Unstable tracking task. After a brief rest, the subject was presented with an unstable tracking task on a television monitor (CRT) (Jex, McDonnell, & Phatak, 1966). This task places variable demands on human information processing resources dedicated to the execution of rapid and accurate manual responses. During this task, the subject viewed a small, fixed target area in the center of the CRT. A cursor moved vertically from the center of the screen and the subject's task was to attempt to keep the cursor centered over the target area by left and right movements on a hand held control stick. The active area of the display was ± 9.5cm, and average luminance was 30-35 foot-lamberts. The task is unstable in that the

subject's input introduces error into the system which is magnified--resulting in increasing necessity to respond to the velocity of the cursor movement as well as to cursor position. If the subject lost control and the cursor traveled to the edge of the display, it was automatically reset to the display center and the subject continued tracking. The test battery generated measures of tracking error and control losses as dependent variables. The subject was presented with two trials (three minutes each) corresponding to two different experimenter controlled demand levels that varied the manual control difficulty. Additionally, the task was programmed to cause the moving cursor to blink off every six seconds and reappear 200ms later. In this manner, the test battery recorded a transient evoked response to approximately 30 blinks from 150ms before to 850ms after blink onset and stored them for future analysis.

Short term memory task. The subject was given a brief rest, and his attention was again directed to the CRT for presentation of the short term memory task (after Sternberg, 1969). The subject was then told that he would be presented with a single two digit number in the center of the screen which he was to memorize. When the subject indicated that he was ready, software presented random two digit numbers (the negative set) some of which were the memorized number (positive set). The subject was told to decide as quickly and as accurately as possible to which set the number belonged, and to indicate his choice on a hand held response box. The subject was given as much time as necessary for memorization and was told not to blink during number presentations. After the presentation of 40 numbers and a brief rest, the program was recycled to present a three-number and a five-number memory set following the same procedure. Each

number was approximately 20mm wide and 12mm high with an average luminance of 35 foot-lamberts. Each number was on the screen for 200ms and the interstimulus interval was randomly generated to between 1.5 and 2 seconds. The proportion of positive to negative numbers was 50:50 resulting in 20 positive and 20 negative trials for each memory set. Two digit numbers were used to avoid the repetition of any number during the practice or the four experimental runs. During the presentation of each memory set, the microprocessor stored the response to each letter in terms of correct/incorrect and the reaction time from the onset of each letter to the button press. These data were also sent to disc for later analysis. In addition, a trigger pulse was generated to the onset of each number, both positive and negative, which caused the test battery to record both electroencephalographic and eye blink responses for 850ms after stimulus appearance. These data were also stored on a temporary disc for later analysis. Run time for this task was approximately 5-6 minutes.

Spatial processing task. The subject's attention was again directed to the CRT screen for the Criterion Task Set (Shingledecker, 1984) spatial processing task. This is a standardized loading task designed to place variable demands upon information processing resources required for the manipulation and comparison of spatial information. This task required the subject to view a series of 23 to 28 pairs of histograms presented one at a time. The subject was told to decide whether the second histogram in each set of two (the comparison item) was identical to the first (the target item) and to respond either positively or negatively by means of a hand held response box. The proportion of "same" to "different" was approximately 50:50. The demands of the task were manipulated by varying the

number of bars in the histograms and the spatial orientation of the comparison histogram. In the low demand presentation, a two bar histogram was presented with the comparison item in a 0-degree orientation. The task took approximately three minutes to perform with targets displayed for three seconds each followed by the comparison targets displayed for 1.5 seconds each. Measures of both speed (reaction time) and accuracy (error rate) were generated and stored. Additionally, the transient evoked potential was generated from the display (the onset of each comparison histogram) and resulted in a cognitive evoked response, P300, to each decision point. All EEG and eye movement data were recorded from 150ms before to 850ms after each stimulus and stored by the test battery for analysis. After the low demand presentation, the program presented a high demand condition (six-bar stimuli with the comparison histogram rotated 180°). Histogram bar length was between .85 and 5.11cm high. Bars were .5cm wide and were separated by .4cm spaces. Luminance levels of the two and five bar histograms were approximately 33 and 48 foot-lamberts respectively.

Steady state evoked response to patterned stimuli. Next, the low frequency steady state evoked response was collected. The subject's attention was again drawn to the television screen. An SRL Checkerboard Generator was used to produce a full screen black and white checkerboard pattern with checks .7 cm square. The subject was told to fixate on the center of the screen while the pattern was set to flicker 7.5 Hz for approximately one minute. Measurement did not begin until 10 seconds after the stimulus had begun to flicker in order to allow the brain time to settle into a steady state response condition. A Nicolet CA 1000 Clinical Signal Averager was used to analyze the occipital EEG. The evoked potential consisted of the

average to 64 samples--each triggered on the first stimulus flicker after completion of data collection for the previous sample. Sweep epoch time was 500 msec. At the completion of the 64th sample, the average was stored in one of four channels of internal memory in the CA 1000. The subject was given a brief rest, and the checkerboard was set to flicker at 10 Hz for another 64 samples. When that average was stored, the flicker rate was set at 15 Hz for the third and final 64 sample average. As backup to the Nicolet, raw EEG was recorded to each frequency presentation. Unlike any of the tasks preceding it, the averaged response was not stored for future analysis. This required the experimenter to set the CA 1000 to plot the averaged waveform for each stimulus frequency and to manipulate a cursor in order to label each peak of interest with its amplitude and latency in order to free the memory of the CA 1000 for the next subject's data. This was done, however, after each subject's completed run.

Transient visual evoked response. The transient visual evoked response was next generated using a Grass Model PS-22 Photostimulator. The face of the strobe light was 13.3 cm in diameter, with an average intensity of 4.8×10^3 foot-lamberts at the lamp. The strobe was set to flicker at 1 Hz and the subject was told to fixate on the center of the lamp, blinking only during the inter-flash interval, until told to stop approximately 1.5 minutes later. During stimulation, 500 msec samples of EEG were triggered to the onset of each of 100, two microsecond flashes. The samples were averaged by the CA 1000 and the averaged waveform was stored in its fourth memory channel for amplitude and latency measurement between subject sessions.

Critical flicker fusion threshold. The final task determined the critical flicker fusion threshold frequency. The subject was told to close his eyes as the experimenter increased the strobe flicker rate to 10 Hz. From there, the experimenter increased the flicker rate in 1 Hz increments per second. The subject was told to raise his hand when the light seemed to stop flickering and became a steady, fused light. The frequency at which the lamp was flickering when the subject raised his hand was then recorded. The lamp was then increased to its maximum flicker rate. The experimenter then decreased the flicker rate by the same increments and the subject was told to raise his hand at the first perception of flicker. That frequency was also recorded and the average of the two was calculated and taken as the critical flicker fusion frequency.

RESULTS

Subjects were administered the series of tasks described above and generated the measurement of 93 separate dependent variables per subject during each of the four measurement sessions. Raw data were tabulated, sorted, and subjected to a multivariate analysis of variance for repeated measures using BMDP 4V. This particular analysis package generated group means for each variable over the four measurement sessions, along with their associated covariance matrix, and an overall significance level for differences in the dependent variable. A subroutine in this package also can be used to yield a multivariate contrast statistic, Hotelling's T^2, for any comparison of interest. In the previously mentioned pilot study (Rizzuto et al., 1984), the full capability of the 4V multivariate analysis was used to test for several differences critical to the hypotheses of the study. The hypotheses were that the baseline measures for each variable would not differ significantly either from each other or from the placebo measurement. Accordingly, multivariate comparisons were made in the pilot study between each day's baseline measurement (Baseline Day 1 vs Baseline Day 2) and between each baseline and the placebo measurements (Baseline Day 1 vs Placebo; Baseline Day 2 vs Placebo). Matrix manipulations were then used to convert these T^2s to exact F statistics and calculate their associated probabilities. The resulting matrix of probability values confirmed that there were no significant differences between the pilot's baseline measurements or between the placebo and each day's baseline. Thus, it made sense to average the pilot study's baseline means with its placebo means and to make the final comparison of the average of these three with the means of the diazepam ingestion session.

Since the present study was basically a replication of the pilot study, and the previously mentioned hypotheses were confirmed, the multivariate contrasts between the baselines and the placebo measurement were not repeated in the present analysis. Instead, the comparison was made between the average of the baseline and placebo data and the diazepam data. Note, therefore, that this portion of the present analysis amounts essentially to a paired t-test (df = 1, 27) between the diazepam ingestion measurements and the averaged means of the other three measurement conditions.

Visual Tests

The individual means for the components of the visual tests are presented in Table 1 along with their associated probability values.

The mean coherence function of the steady state visual evoked response to unpatterned stimulation reflects a gross correlation between the spectral analysis of the three input frequencies in each stimulus category (low, medium and high) and the spectral analysis of the resulting brain response. In short, the coherence function reflects how much of the brain's output is due to the stimulus input. That no significant valium-induced decrements in the coherence functions were found indicates that the cortical ability to process low, medium, and high frequency unpatterned visual stimulation was unaffected by the 10mg dose.

The apparent latency or transmission speed of the visual cortex was also obtained from the unpatterned steady state response. The test battery

TABLE I

Group means and associated p values for visual tests

Measure	Frequency/ Component	Baseline 1	Placebo	Baseline 2	Diazepam	p
Steady State Mean Coherence	Low	.1864	.2029	.2196	.2076	.84
	Med	.3385	.3376	.3668	.2738	.06
	High	.1498	.1475	.1488	.1269	.17
Steady State Transmission Speed (msec)	Low	126.3	138.7	143.0	213.1	.0001
	Med	105.9	121.4	123.2	158.0	.006
	High	95.2	95.0	100.3	150.7	.0009
Checkerboard Amplitude (uV)	7.5Hz	8.77	8.63	8.86	7.28	.0001
	10Hz	7.64	7.96	7.97	6.78	.0029
	15Hz	4.90	4.87	5.16	4.37	.0232
Checkerboard Latency (msec)	7.5Hz	114.4	113.5	113.8	122.9	.0004
	10Hz	28.07	29.0	27.93	36.64	.0184
	15Hz	49.86	51.14	49.14	56.14	.0072
Strobe Amplitude (uV)	N1, P1	9.07	8.60	9.57	7.56	.0020
	P1, N2	8.27	8.05	8.85	6.43	.0020
	N2, P2	8.86	8.77	8.70	6.24	.0001
	P2, N3	8.41	8.07	8.61	6.04	.0001
Strobe Latency (msec)	N1	63.36	64.36	62.29	71.71	.0119
	P1	103.4	103.7	105.0	116.4	.0001
	N2	147.0	146.1	151.0	162.0	.0001
	P2	209.1	208.3	209.3	227.4	.0001
	N3	291.6	289.4	294.6	312.5	.0002
CFF	Cycles per Second	25.59	25.96	25.18	25.82	.5704

used a Fast Fourier Transformation algorithm to calculate an ensemble average of the cross spectrum for the EEG channel (the cross spectrum is between the EEG channel and the digitized stimulus input channel). From the resultant complex ensemble average cross spectrum the phase lag was calculated for each of the three stimulating frequencies within a class. A straight line curve fit using linear regression was calculated using the three phase lag values. The brain's latency was then determined by dividing the slope of the regression line by 2π. As can be seen in Table 1, highly significant delays in visual cortex transmission speed, ranging from 54 to 77 msec, were obtained following diazepam ingestion. This information, coupled with the lack of change in the coherence function, indicates that although the ability of the visual cortex to process unpatterned visual stimulation is left intact under the influence of the diazepam, its ability to transmit that processed information is significantly slowed.

The low frequency steady state evoked response to patterned (checkerboard) stimuli yielded measures of both amplitude in microvolts (uV) and latency in milliseconds. The brain's characteristic output to the checkerboard stimulus is a sinewave containing a number of positive going peaks. The number of peaks in a particular tracing is roughly equivalent to half of the stimulating frequency (the frequency at which the checks are flickered). Therefore, the three stimulus frequencies yielded sinewave outputs of three, five, and seven peaks respectively (see Appendix A, Figure 1A, B and C). Absolute peak-to-trough amplitude measures were made on each peak and an average amplitude was calculated for each stimulus frequency. As shown in Table 1, and in Appendix B (Table 6), significant

amplitude decreases of between .61 and 1.47 uV were obtained for all frequencies in the diazepam condition. Again, note that the decreases represent the difference between the average of the baselines and placebo means (hereafter referred to as averaged baseline data or simply, as a baseline level) and the diazepam mean. Although not presented in the tables, it is often helpful to look at such decrements in terms of the percent change from baseline (a practice that will be continued throughout the paper). The decrements reported above represent a drop in average amplitude of between 12% and 17% from baseline levels.

The latency of the evoked response to the checkerboard stimulus was measured at the first complete positive peak on each trace. Significant diazepam induced latency increases were observed in each of the stimulus frequencies. As can be seen in Table 1 and in Appendix B, Table 6, the largest latency increase (9msec) occurred in response to the 7.5 Hz flicker while smaller increases were observed in the 10 and 15 Hz condition (8.3 and 6.1msec respectively). These findings further corroborate the transmission speed deficits found in the response to the unpatterned stimului reported above.

In a similar fashion, amplitude measurements of the transient evoked response to the stroboscopic stimulation were taken. However, since with the strobe the precise time of stimulus onset is known and the characteristic output trace has several distinct peaks (see Appendix A, Figure 1D), each component peak is measured individually from its associated trough. With a visual transient response and a noncognitive task, the peaks of interest are those reflecting primary sensory input qualities such as

intensity, pattern sharpness, and color. Since these peaks generally occur within the first 300msec after a discrete stimulus, five peaks identified by their order in the trace and by a letter indicating their direction (P = positive, N = negative) were measured. As can be seen in Table 1 significant amplitude decrements were obtained in all peaks under the diazepam condition. The amplitude decrements ranged from 1.5 to 2.5 uV and reflect an amplitude drop due to the diazepam-exposure of between 17% and 29% from baseline levels.

These results most likely indicate effects on the cortical channels used in processing information regarding intensity. Since the latency of each of the five peaks was also significantly increased (ranging from 8.4 to 20.6msec) further evidence of slowed neuronal transmission in the visual pathways was found.

The final visual test to be analyzed was the critical flicker fusion frequency. The average of the ascending and descending fusion frequencies was calculated and remained extremely close during each of the four measurement sessions. As a result, no significant critical flicker fusion (CFF) changes were obtained after diazepam exposure. Possible reasons for this result, particularly surprising since all previous tests indicated severe decrements in visual sensory function, are presented in the discussion below.

Auditory Discrimination Task

The means and associated probability values for the components of the auditory discrimination task are presented in Table 2. Upon command, the test battery retrieved the individual one second EEG epochs from the temporary disc and averaged the transient parietal responses to both the rare (high) and frequent (low) tones. It then displayed both of the averaged waveforms on its video monitor accompanied by both the amplitude and latency of the highest peak in the epoch (see Appendix A, Figure 2). A separate channel was used to store and display the concurrently averaged electroculographic (EOG) data. The peak of interest in this primarily cognitive task was, of course, the P300. Although the battery could have been set to label the highest peak within the generally accepted range of the P300 (250-300msec), major diazepam-induced decrements in cognitive processing which could result in the P300 occurring outside of these limits were anticipated. Therefore, the battery was set to yield the amplitude and latency of the highest peak in the entire one second average. EOG averages were then displayed and studied to ensure that eye movements and other muscle contamination capable of artifactually yielding high amplitude peaks in the parietal EEG, and therefore being mistakenly identified as the P300, were either absent or far enough removed from even the extended P300 "window" as to be implausible (i.e., from 150msec before to 250msec after the stimulus). When such an implausible peak was discoverd, the battery display was set to a search mode which allowed the experimenter to manipulate a cursor to yield the amplitude and latency of the highest peak within the plausible area beyond 250msec post stimlus. P300 amplitudes in

TABLE 2

Group means and associated p values for auditory discrimination task

Measure	% Correct/ Tone Set	Baseline 1	Placebo	Baseline 2	Diazepam	p
P300 Amplitude	Rare Tone	15.02	13.72	15.63	11.15	.0008
(uV)	Frequent Tone	4.09	3.98	4.57	2.81	.003
P300 Latency	Rare Tone	355.0	356.6	346.8	415.7	.0001
(msec)	Frequent Tone	334.3	337.7	331.8	415.7	.0001
Per cent Correct	%	97.57	96.89	97.71	87.46	.0007

response to both the rare and frequent tones were significantly reduced by diazepam exposure. Amplitudes to the rare, counted tones were much higher than those of the frequent tones as a result of their identification as a critical event. The average decrements to the rare and frequent tones were 3.6 and 1.4 uV respectively (see also Appendix B, Table 7). These correspond to amplitude reduction of 25% and 33% from the pre-drug baseline levels. Significant P300 latency increases were also obtained to both the rare and frequent tone presentations in the diazepam condition (62.9 and 81.1msec respectively). Thus, on the basis of the evoked response alone, cognitive processing in the auditory modality as well as the time required for decision making were severely affected by diazepam. The significant decrement in the percent correct measure, derived by comparing the subjects' reported count to the actual battery generated count, supports this finding.

Unstable Tracking Task

The group means and associated probability values for the unstable tracking task are presented in Table 3.

As with the auditory discrimination task, the test battery was set to retrieve the individual 1 second EEG epochs generated by the stimulus (for this task, the blinking cursor), average them together, and display the averaged waveform (see Appendix A, Figure 3). Since this was a tracking task and therefore, primarily behavioral in nature rather than cognitive, the transient occipital evoked response and its associated peaks were evaluated. Since eye movements were to be fairly constant in this task,

TABLE 3

Group means and associated p values for CTS Unstable Tracking Task

Measure	Condition/ Component	Baseline 1	Placebo	Baseline 2	Diazepam	p
Tracking Error	Low	4.179	3.00	3.393	11.43	.0004
	High	11.36	12.39	11.07	19.00	.0008
Edge Violations	Low	.250	.1429	0.0	3.25	.006
	High	2.036	2.786	2.143	19.86	.004
Amplitude	N1, P1	2.20	2.35	3.23	2.21	.225
(Low Difficulty)	P1, N2	3.91	4.14	4.74	3.17	.002
(uV)	N2, P2	5.79	5.24	5.98	3.82	.0002
	P2, N3	4.02	3.56	4.03	2.95	.032
Latency	N1	117.3	119.6	121.1	148.8	.0001
(Low Difficulty)	P1	156.8	158.4	158.0	197.0	.0001
(msec)	N2	204.5	211.3	207.9	250.0	.0001
	P2	278.7	280.2	282.3	330.0	.0001
	N3	331.6	330.0	333.8	383.8	.0001
Amplitude	N1, P1	3.42	2.95	4.58	3.37	.80
(High Difficulty)	P1, N2	4.71	4.05	6.11	3.91	.13
(uV)	N2, P2	6.02	5.49	6.33	4.77	.07
	P2, N3	4.65	3.86	5.06	3.86	.20
Latency	N1	114.6	118.6	112.7	141.1	.004
(High Difficulty)	P1	154.1	161.8	152.0	184.6	.0016
(msec)	N2	200.7	208.4	208.8	233.8	.0024
	P2	269.8	275.0	275.4	311.4	.0001
	N3	323.7	323.4	329.1	364.1	.0001

the amplifiers were set to filter out most high frequency noise. Even so, the same care was taken as with the auditory discrimination task to view the concurrently averaged EOG channel to account for any muscle artifact that could affect the transient response. This task was also unique in that while it was recording the transient evoked response and EOG in response to the cursor blinks, it also kept a running count of the number of times the subject lost control of the cursor (resulting in its leaving the edge of the screen), and calculated an average absolute tracking error based on the displacement of the cursor from center measured every 21msec during the task (see Shingledecker, 1984 for calculation formulae). Looking first at the behavioral data, both mean tracking error and the number of edge violations increased significantly after diazepam ingestion. Tracking error in the low and high condition increased an average of 7.9 points and 7.4 points respectively (see also Appendix B, Table 8), representing increases of 224% and 63%. Edge violation showed an increase of 3.12 points for the low and 17.54 points for the high condition, representing increases in excess of 2000% and 600% respectively. These performance results indicate deficits in perception and in manual responsiveness, echoing the performance decrement in the auditory modality. The neurological basis for these tracking decrements can be found in the evoked response results. Amplitudes and latencies were measured in the same manner as for the strobe transient described above. As can be seen in Table 3 significant amplitude decrements occurred to all peaks in the low difficulty condition except the N1, P1 complex. The significant decrements ranged from .92 to 1.85 uV, representing a decrease in amplitude of between 24% and 33%. The N1, P1 complex decrement was .383 uV representing a 14.7% post-drug amplitude decrease. The high difficulty condition produced no

significant amplitude decrements in any of the measured peaks. Amplitude changes ranged from .28 to 1.2uV, representing post diazepam amplitude decrements of between 7% and 20%. Latency decrements, on the other hand, were found to be highly significant in both the low and high difficulty conditions. Low difficulty diazepam latencies increased on the average between 29.5 and 51.6msec, representing changes of 16% to 25% from baseline levels. Latencies in the high difficulty position increased an average of 26 to 39 msec reflecting a 12% to 22% change from baseline. These transient evoked response latency increases are in accord with the previously described strobe latency data, and support a general slowing of visual cortex transmission speed which is also reflected by the behavioral error performance decrements. However, the superimposition of the active tracking task caused a response in the amplitude measures that was different from the strobe transient, as only the low difficulty condition amplitude changes achieved significance. The fact that the transient amplitudes in the tracking task seem less affected by the drug than by the difficulty condition has interesting implications that are discussed below.

Short Term Memory Task

The group means and probability values for the short term memory task are presented in Table 4. The analysis of this task is comprised of eight sub-analyses. The response time to each of the 40 stimulus numbers for each of the three memory sets, measured from the onset of each number to the button press, was provided by the battery and tagged with either a (+) for correct or a (-) for incorrect. Also provided by the battery were the number wrong, the resulting per cent correct, the mean reaction time, and

TABLE 4

Group means and associated p values for short term memory task

Measure	Memory Set	Baseline 1	Placebo	Baseline 2	Diazepam	p
Reaction Time (msec)	Positive Set 1	489.7	473.2	473.1	537.9	.0005
	Positive Set 3	576.9	577.9	571.4	673.3	.0001
	Positive Set 5	619.6	637.3	608.3	755.0	.0001
	Negative Set 1	497.4	501.3	490.3	560.4	.0013
	Negative Set 3	579.5	588.9	588.7	711.8	.0001
	Negative Set 5	636.5	649.4	633.4	797.0	.0001
Per cent Correct	Positive Set 1	97.32	96.96	97.86	93.93	.004
	Positive Set 3	94.64	94.82	95.71	93.04	.15
	Positive Set 5	95.18	92.14	93.93	87.86	.008
	Negative Set 1	97.86	97.86	98.39	97.14	.22
	Negative Set 3	96.61	96.07	96.43	95.0	.31
	Negative Set 5	96.79	96.61	96.25	93.93	.059
P300 Amplitude (uV)	Positive Set 1	12.30	11.74	12.34	9.69	.0014
	Positive Set 3	8.93	8.59	9.36	7.25	.004
	Positive Set 5	7.40	7.19	7.50	6.32	.057
	Negative Set 1	8.53	8.89	8.50	7.11	.0004
	Negative Set 3	7.66	7.01	7.11	5.20	.0004
	Negative Set 5	6.42	5.47	6.43	4.63	.0035
P300 Latency (msec)	Positive Set 1	387.7	388.6	392.3	454.5	.0001
	Positive Set 3	416.4	426.0	411.1	501.3	.0001
	Positive Set 5	423.6	419.8	424.5	495.2	.0001
	Negative Set 1	392.9	398.0	389.6	451.6	.0001
	Negative Set 3	415.2	418.9	420.3	477.3	.0001
	Negative Set 5	411.4	406.8	405.0	490.7	.0001

TABLE 4 (Continued)

Measure	Memory Set	Baseline 1	Placebo	Baseline 2	Diazepam	p
Reaction Time Slope	Positive Sets	32.31	40.12	35.32	54.27	.0001
	Negative Sets	34.67	36.14	35.78	59.15	.0001
Reaction Time Intercept	Positive Sets	464.3	444.1	448.9	501.5	.006
	Negative Sets	466.1	469.9	463.4	513.0	.03
P300 Latency Slope	Positive Sets	16.87	16.90	14.85	19.25	.03
	Negative Sets	15.35	14.38	13.99	20.32	.007
P300 Latency Intercept	Positive Sets	382.3	388.0	385.2	453.1	.0001
	Negative sets	392.6	401.4	393.5	443.9	.0001

the standard deviation for both the positive (memorized) and negative (non-memorized) number sets. As stated previously, each number was on the screen for 200 msec and the interstimulus interval was between 1.5 and 2 seconds. On several occasions, subjects failed to respond to the stimulus number within the allotted time. When this occurred, a manipulation of the raw data was necessary to delete erroneous individual reaction times in order to recompute a more accurate mean reaction time. A detailed description of this procedure is presented in Appendix C. As shown in Table 4, the reaction times to all positive and negative memory sets were significantly affected by the diazepam. Average increases ranged from 52msec to 153msec (see also Appendix B, Table 9), increasing monotonically as the memory set size increased, and reflecting increases of 10% to 22% from baseline reaction times.

In spite of the decrements in reaction time, the percent of correct responses remained relatively unaffected by the diazepam, achieving significant decrements in positive sets 1 and 5 only. The average decrements in the nonsignificant sets ranged from .89 to 2.6 percentage points reflecting differences of only .9% to 2.7% from baseline levels. The decrements for positive sets 1 and 5 were 3.5 and 5.9 percentage points respectively, reflecting differences of 3.5% and 6.3% from the baseline levels. Apparently, adequate short term memory performance was largely maintained although the time required to respond to the numbers was significantly increased. As in the auditory discrimination task preceding it, the average parietal transient evoked response to the onset of the different stimuli was displayed by the test battery, allowing the amplitude and latency of the P300 response to both the positive and negative set

numbers to be measured for each difficulty level (see Appendix A, Figure 4). The P300 amplitude decreases in the diazepam condition achieved significance for all memory sets except positive memory set 5, which barely missed statistical significance ($p = .057$). Amplitude decrements for the significantly different memory sets ranged from 1.7 to 2.4 uV reflecting decreases of 18% to 28% from predrug baselines. Although the amplitude decrement for positive set 5 was 1.04 uV, this reflected a drop of only 14% from its baseline.

The latency of the P300 for each of the positive and negative memory sets was measured from stimulus onset and was found to increase to a highly significant degree following diazepam ingestion. Latency increases ranged from 64 to 83msec in the positive sets and from 58 to 83msec in the negative sets, representing an average increase of 14% to 20% over baseline levels. Thus, for the most part, the reaction times and P300 amplitudes and latencies were significantly affected in the diazepam condition, while the per cent correct, i.e., the ability to discriminate between a memorized and nonmemorized number, was affected in only 2 of the 6 memory set conditions. To shed further light on the exact cognitive processes being affected in this task, linear regression was used to calculate the slopes and intercepts of both the reaction time and the P300 latency data. Sternberg, (1969), upon whose memory scan paradigm this task was based, has interpreted the y intercept of the reaction time vs. set size function as reflecting the time required for encoding the raw stimulus, comparing it with all the stimulus alternatives in the memory set, categorizing the stimulus as either positive or negative, and selecting the appropriate response. In short, the intercept reflects the input/output time required

for the above stages. The slope of the same function represents the rate at which the comparison process in the second stage proceeds.

As can be seen at the bottom of Table 4, both the reaction time slopes and reaction time intercepts increased significantly after diazepam ingestion - providing support for the reaction time and P300 latency shifts. The slope for the positive sets increased 18.4 points or 51% from the baseline slope values and the negative set slope increased 23.6 points, reflecting a 66% increase from its baseline levels. The intercept for the positive sets increased 49.1 points or 11% from baseline levels, and the negative set intercept increased by 46.5 points, reflecting a 10% increase from its baseline. Finally, as a backup to the reaction time slope and intercept data, slope and intercept values for P300 latency were also calculated and compared for similar effects. As can be seen, the P300 slopes and intercepts for both positive and negative sets showed significant increases as well. The slope value for the positive sets increased by 3.0 points or 18% from baseline levels and the negative set slope increased by 5.8 points, reflecting a 39% increase from its predrug baseline. The intercept for the positive sets increased 67.9 points or 18% from baseline levels and the negative set intercept increased 48.1 points, reflecting better than a 12% increase from its baseline.

Spatial Processing Task

The group means and associated probability values for the spatial processing task are presented in Table 5. As in the short term memory task preceding it, a computer printout of the behavioral data was generated.

TABLE 5

Group means and associated p values for CTS Spatial Processing Task

Measure	Difficulty Condition/ Component	Baseline 1	Placebo	Baseline 2	Diazepam	p
Per cent correct	Low	92.25	91.52	90.84	89.93	.22
	High	91.99	91.33	90.74	92.89	.13
Reaction Time (msec)	Low	619.0	588.2	624.4	704.6	.0001
	High	985.9	954.3	1027.4	1124.0	.005
P300 Amplitude (uV)	Low (same)	9.34	9.33	9.16	6.63	.002
	High (same)	6.22	6.21	7.05	5.34	.034
	Low (diff)	9.28	8.17	9.71	6.65	.0003
	High (diff)	6.33	6.02	7.11	4.43	.0002
P300 Latency (msec)	Low (same)	375.7	381.3	374.8	443.9	.0001
	High (same)	405.7	403.9	407.0	477.9	.0001
	Low (diff)	391.1	387.3	400.0	462.7	.0001
	High (diff)	406.1	399.3	413.9	471.6	.0001

These data included the mean reaction time for an entire low or high difficulty measurement session (without differentiation as to whether the comparison stimulus was the same as or different from the target stimulus), the standard deviation, the number of stimuli presented, the number correct and resulting percent correct, and the number of stimuli not responded to within the time limit.

As shown in Table 5, the reaction times for both the low and high difficulty conditions were significantly increased after diazepam ingestion. Reaction times in the low difficulty condition increased an average of 94.1msec reflecting a 15% increase from baseline levels. The reaction times for the high difficulty condition increased 134.9msec reflecting a slightly smaller 13.6% increase from predrug levels. However, as in the task preceding it, the performance of the task as reflected by the percent correct measure was adequately maintained. The percent correct for the low difficulty condition decreased by only 1.61 percentage points yielding a 1.7% change from baseline levels and failed to reach significance. The percent correct for the high difficulty condition actually increased 1.54 percentage points reflecting a 1.7% difference from predrug levels but also failed to reach statistical significance.

Finally, both the amplitude and latency measures of the P300 response to the low and high difficulty conditions were all significantly affected by the diazepam. In this analysis the test battery was able to average not only the responses to the low and high difficulty histograms, but also generated separate transient averages for the histograms that were either the same or different from the target histogram in each condition (see

Appendix A, Figure 5). The amplitude of the low and high difficulty condition P300 when the comparison histogram was the same as the target histogram decreased 2.6 and 1.2 uV respectively, reflecting a decrement of 28.6% and 17.75% from baseline amplitude levels (see Appendix B, Table 10). The amplitudes of theP300 response to the same difficulty levels when the comparison stimulus was different from the target stimulus decreased 2.4 uV in the low difficulty condition, and 2.1 uV in the high difficulty condition. These amplitude changes resulted in decrements of 26.5% for the former and 31.75% for the latter from their respective predrug baselines.

The P300 latency in the low and high difficulty conditions when the comparison histogram was the same increased 66.6msec in the low condition, yielding a 17.6% increase from baseline, and 72.4msec in the high condition, reflecting a 17.9% increase from baseline levels. When the comparison histogram was different from the target, the latency in the low difficulty condition increased 69.9msec resulting in a 17.8% rise from baseline. For the same comparison in the high difficulty condition, P300 latency increased 65.2msec yielding a 16% rise from its predrug level. Again, the P300 amplitude and latency as well as the reaction time were all significantly affected while performance of the task remained intact.

Power Calculations

Power calculations were derived for the subtests in each category in the manner described by Morrison (1976) for use in multivariate hypothesis testing. A noncentrality parameter was first calculated for each subtest using matrix algebra procedures. The variables used in its derivation were

(a) the number of subjects, (b) the squared difference between the averaged means of the baseline and placebo measurements and the diazepam measurement, and (c) the pooled covariance matrix. Probability functions were then used to calculate the power of each subtest based on its noncentrality parameter, its corresponding degrees of freedom, and a fixed alpha level of .05. Tables 6 through 10 appear in Appendix B and represent the power findings for the subtests of the visual, auditory discrimination, unstable tracking, short term memory and spatial processing tasks respectively. The mean difference between conditions, their accompanying standard deviation, and the noncentrality parameter values precede the power value. A negative value in the mean difference column reflects an increase in the dependent variable of interest, and a positive sign reflects a decrease. As shown in the charts, power was generally high for the obtained differences and standard deviations across subtests. The implications of these calculations are considered below.

DISCUSSION

The test battery provided excellent stimulus presentation, response storage, averaging, and measurement of many of the human responses to minor tranquilizer ingestion. The overall analysis of the results showed a consistent, generalized depressant effect of the 10mg oral dose of diazepam on most of the physiological, cognitive, and behavioral variables considered in this study. The more basic, sensory tasks reflected amplitude decreases and latency increases in the visual evoked potential indicative of slowed central nervous system functioning. Variable difficulty behavioral tasks performed and measured concurrently with the degraded evoked potential

showed both increased reaction time and increased errors. Tasks that were more cognitive in nature requiring matching to memory, spatial processing and auditory discrimination, generally showed similar degradation in both the latency of the cognitive evoked response and reaction times but showed a greater degree of variability in terms of amplitude and other concurrently measured performance indicators. Because of the large number of variables to be considered, the discussion is divided into sections grouping evoked potential variables related to basic sensory/physiological function, including those measured concurrently with a behavioral task; auditory evoked potential variables measured concurrently with a "passive" cognitive task requiring no behavioral response; and finally the visual evoked potentials measured concurrently with the more active cognitive tasks requiring both decision and timed behavioral response.

Since the psychopharmacological action of diazepam is one of presynaptic inhibition, primarily a latency factor, delays in cortical transmission time are a logical consequence. In this experiment, significant delays as well as amplitude decrements were measured from the visual cortex in response to a transient light flash (strobe), a flickering patterned stimulus (checkerboard), and a higher frequency unpatterned light stimulus (flourescent tubes). In considering the amplitude and latency changes to the pattern reversing checkerboard following diazepam ingestion, it is necessary to keep in mind that this measure has been used extensively in clinical medicine as an indicator of various visual system pathologies (Aaselman, Chadwick, & Marsden, 1975; Celesia & Daley, 1977; Halliday, Barrett, Halliday, & Michael, 1977). Abnormalities in the evoked response to patterned stimuli seem not to be specific for a given disease, but,

rather, indicate a disturbance of function somewhere along the visual pathways. The amplitude of this evoked response is decreased by any process producing a change in visual acuity or by poor fixation on the stimulus field, and its latency is increased by any process increasing synaptic transmission speed. Astigmatism, glaucoma, amblyopia, certain forms of optic neuritis, and multiple sclerosis have all been found to produce decreased amplitude and increased latency in the pattern-evoked response (see Chiappa & Ropper, 1982 for a review). Interestingly, many of the observed changes in the evoked response precede any subjective awareness or clinically observable signs of visual system dysfunction - thus their usefulness as early indicators of progressive pathology. The frequency range of stimulation that produces the most consistent and stable results in terms of latency increases is the medium frequency range. For example, in multiple sclerosis, the medium frequency evoked potential signals are delayed, while higher frequency evoked potentials seem unaffected. Regan (1975) hypothesized that since both signals travel the same optic nerve these data support the existence of different classes of frequency-sensitive axons that are differentially affected by the disease. That diazepam significantly affected latencies in this test across all three frequency classes indicated a more global depression of the visual pathways responsible for the transmission of patterned information. That the measured degradation was substantive is further reflected by the amount of the delay. Postingestion delays in latency were between 6 and 9msec. Regan, Milner, & Heron (1976) have reported delays in pattern flicker evoked potentials of between 2 and 9msec for multiple sclerosis patients between 1 and 12 years from the onset of the disease.

As for the integrity of the pattern being transmitted, amplitude decrements can be considered independently from latency decrements. These decrements normally indicate more of an acuity or attentional deficit, and can occur with or without delays in neurological transmission. (Marg et al., 1976; Regan, 1975; Starr, Sohmer, & Celesia, 1978). The significant amplitude decreases in the patterned evoked potential in the present study are most likely the result of both attentional and acuity decrements caused by diazepam but enhanced by the task demands. Although subjects' faces were monitored by means of the television camera, and no obvious attentional or gaze fixation problems were noted, most subjects reported feeling the classical effects of tranquilizer ingestion, including increased relaxation, drowsiness, and decreased muscle tone. These, in turn, resulted in a decreased ability to keep the eyes continuously fixated on the center of the screen for the time required. Various random illusions of movement (both horizontal and vertical) are created on the screen as the checks are flashing and it requires a conscious effort to resist following their movement and to focus one's attention on center screen. Most subjects reported increased difficulty in doing so after diazepam ingestion. Likewise, several subjects also reported difficulties in keeping the checks in focus for the entire test period as their attention waned. Therefore, the postdrug amplitude decrease can be attributed to both the increased difficulty in keeping attention and gaze fixated on center screen and, for some subjects, to the additional acuity decrements caused by periodic defocussing.

Latency increases and amplitude decreases were observed also in the transient evoked response to the strobe stimulus which, of course, is

unpatterned and stimulates the visual system at a much slower rate - allowing a discrete "on-off" neuronal response rather than the entraining of the brain's response to any particular, continuous frequency. Many lines of evidence (summarized by Beck, 1975) have indicated that the components of the transient evoked response prior to about 250-300msec reflect the physical, qualitative aspects of the stimulus such as color, intensity and sharpness while the later components showed sensitivity to the meaningfulness of the stimulus to the subject. Since the transient stimulus in this study was unpatterned, and color and intensity remained constant, the significant amplitude decrements observed most likely reflect a decreased responsiveness in the cortical channels sensitive to the transmission of information regarding light intensity. These results are in agreement with evoked potential data reported by Ebe, Meier-Ewert, and Broughten (1969) investigating intravenous diazepam and photosensitivity in both epileptic and normal subjects. However, those authors reported consistent amplitude decreases in the earlier components only, either with or without latency increases, and more variable results in later components. The results were reported as consistent with animal findings where intracranial recordings made at the chiasma, lateral geniculate body, and striate cortex indicated diminished retinal discharges to the strobe flash after valium injection. The present findings indicate a more consistent reduction in amplitude that was always accompanied by a latency increase in all components. Although discrepancies in these two sets of data may be due to differences in equipment and recording techniques, a detailed description of the same is absent in the above-mentioned study, precluding a direct comparison. However, it is sufficient to say that both sets of data indicate an inhibition of cortical activity related to unpatterned visual information as measured by

the evoked potential amplitude decreases, a finding that is consistent with the action of the drug used. Further, the latency increases in these transient data are consistent with the latency increases measured in response to the patterned steady state data - yielding further indications of a global decrease in synaptic transmission speed due to diazepam exposure.

As reported earlier, the high frequency steady state evoked potential to unpatterned visual stimulation also yielded results directly interpretable as a significant neurological transmission speed delay. Regan (1975, 1977a) used this technique of combining several frequencies of light into a single complex waveform and measuring the slope of the phase lag versus stimulus frequency in several clinical studies. As a result, significant retinocortical delays were found in patients suffering from both multiple sclerosis and retrobulbar neuritis. Interestingly, he reports a mean transmission speed from control subjects of 120ms in response to medium frequency unpatterned flicker and a classification of abnormality if the difference between an affected and unaffected eye exceeded 10ms. In the present experiment, baseline transmission speeds averaged about 116msec, in line with the above findings, and were accompanied by a significant post-ingestion delay of over 41msec. Similar, though larger, delays measured in response to low and high frequency unpatterned stimulation further support our transient and patterned evoked response delay findings. However, since the mean coherence function was not significantly affected by the diazepam, the integrity of the transmission, though slowed, remained largely intact, indicating that the processing of different frequencies of unpatterned stimuli was less affected by the 10mg dose. This finding is also supported

by Regan's (1975) experiments in which he reports that the amplitude of the responses in his patient population could remain unaffected in tne presence of large latency increases. To our knowledge, this experiment represents the first attempt to use this method for the purpose of measuring neurological delay in response to a depressant drug.

Since the critical flicker fusion frequency has been found to alter consistently in response to centrally active drugs, including diazepam (see Kleinknecht et al., 1975 for a review) our findings are clearly inconsistent with reported research. Several possible reasons exist for this discrepancy. Methodological variations such as light intensity, color, light-to-dark time ratios, light diffusing filters, mirrors, artificial pupils, and the postingestion measurement time are all represented in this literature. Since a thorough review is beyond the scope of this discussion, our findings will be compared only to research involving diazepam. Haffner et al. (1973) reported significant depressions of CFF in response to both 10mg and 20mg of oral diazepam at 2 hours 20 minutes and at 5 hours following ingestion. Similarly, Morland et al. (1974) reported a decrement in CFF at about 2 hours after oral ingestion of a 10mg dose. In both cases, the significant decrements were measured after a longer postingestion interval than in this study. Additionally, subjects in both studies were required to fast for 10 hours before drug ingestion and venous blood samples were taken 1 hour and 45 minutes after drug administration. The longer postingestion interval preceded by fasting most likely resulted in more of the drug being metabolized into the system, as contrasted with our study where subjects' CFF was purposely measured last at approximately 1 hour 30 minutes postingestion, and no fasting requirements existed.

Since no blood samples were taken in our study, it can only be hypothesized that less of the drug was metabolized into the bloodstream and that the perception of high frequency unpatterned flicker was unaffected at the time interval measured. The steady state coherence data would seem to support this explanation. Additionally, studies that used intravenous diazepam where metabolism was not a factor (e.g., Grove-White and Kelman, 1971), have reported significant CFF decrements that were maximal within 5 minutes of injection.

In total, the above results indicated consistently slowed neurological functioning in the visual cortex in response to both patterned and unpatterned visual stimuli presented in several frequency ranges. Additional decrements appeared in perceptual variables responsive to visual acuity, attention, and intensity, while the perception of high frequency unpatterned stimulation was left unaffected.

The CTS Unstable Tracking Task allowed further evaluation of drug effects on the transient evoked response, with concurrent measurement of performance variables under two levels of difficulty. In both the low and high difficulty conditions the latency of all evoked response components increased significantly after diazepam ingestion in agreement with the previous data. Since the tracking task was continuous and magnified the subjects' own error, any significant perceptual delay would most likely result in decreased responsiveness and accuracy - particularly when coupled with diazepam's well known depressant effect on the motor system. That such perceptual-motor effects were taking place was further evidenced by the significant increases in both tracking error and edge violations. Since

the eyes were allowed to move, due to the active nature of the task, and there was ample time to blink between stimuli (6sec), no deficits in the ability to keep the stimulus in focus were reported in either condition. Since luminance levels were also kept constant during the task, the overall diminished amplitude of the evoked response in the low difficulty condition was most likely the result of attentional rather than acuity decrements. The low difficulty condition in this experiment was extremely easy to perform. Subjects usually had little difficulty keeping the moving cursor centered in the stationary target area with minimal stick movement. Due to the ease of the task it is likely that the attention allocated to its performance was minimal. Haider, Spong, and Lindsley (1964) were probably the first to establish that as vigilance fluctuated over the course of a behavioral task, the amplitude and latency of the transient evoked response showed corresponding variations. In general, a drop in alertness was followed by reduced amplitudes and increased latencies - particularly if, as in our case, the response was elicited by a stimulus not requiring a response. Fruhstorfer and Bergstrom (1969) found similar results and localized the amplitude decrements to all early components of the evoked response except the earliest positive peak (P1). Our amplitude results are certainly consistent with these findings and indicate that the diazepam lowered an already existing level of decreased alertness.

Conversely, the amplitude levels in the high difficulty condition, although generally diminished after diazepam ingestion, failed to reach significance. It must be remembered that the high difficulty tracking task was the most physically active of all the variables tested. In contrast with the low difficulty tracking condition, the high difficulty condition

required greater stick displacement to maintain control over the cursor, and moved at a much faster pace, due to the test battery's internal magnification of tracking error. That the transient amplitudes were generally higher in the high difficulty condition is consistent with a hypothesis of increased neural activation due to attentional differences in the task. As a result, it seems that although the diazepam increased the latency of the evoked response in the high difficulty condition, as well as in the low, the increased attentional allocation in the former was large enough to overcome the diazepam-induced alterness/vigilance decrements found in response to the latter. However, it is obvious in both conditions that, whether the attentional allocation was high or low, the response degradations due to the perceptual-motor deficits could not be overcome. Thus, it appears that the introduction of a behavioral task during the measurement of the transient revoked response, primarily increasing the attentional and response requirements of the subject, has effects on the amplitude different from those that occur when the sensory peaks are measured in a more passive, noninteractive situation.

The P300 is also a transient neurological phenomenon. It differs, however, from the transient evoked responses discussed above in that it occurs after the primary sensory peaks, and is responsive instead to endogenous cognitive rather than sensory processes (see Beck, 1975 for a review). In fact, both auditory and visual stimuli can be used, or even interchanged within a task, without significant effect on P300. A common use of the P300 is to index the classification of a stimulus as relevant to a task, thereby identifying such a stimulus as a critical event, or non-relevant - requiring no response or processing other than to classify it as

irrelevant to the task at hand. The P300, then, measured from the parietal areas of the cortex, and time-locked to the presentation of both kinds of stimuli, is used to reflect the point of decision (i.e., stimulus evaluation time) via latency and the classification as critical or noncritical via amplitude (see Pritchard, 1981 for a comprehensive review of these and many other classic P300 paradigms). The first measurement of P300 in the present experiment was in response to the auditory discrimination of critical, infrequent high tones from noncritical, but frequent, low tones. As expected, the P300 amplitudes of the noncritical tones were lower than those of the critical tones, indicating a clear ability to distinguish between the critical and noncritical event and to classify them accordingly. The significant amplitude decreases following the diazepam ingestion obviously indicate changes in this ability. The nature of this change is reflected by the P300 latency increases and by the increased error rate, both of which were highly significant. Since this was the longest task in the series (approximately 4 minutes), was performed with eyes closed, and required no overt response, the attentional deficits brought out in the tracking task were in evidence here as well. Subjects reported their minds wandering from the task under the influence of diazepam, losing count of the tones, and missing tones completely before refocusing their attention to the task at hand. Decreased confidence in the classification of the tones and in the tone count itself were the primary results. Interestingly, when asked for the tone count at the conclusion of the trial, most subjects phrased their response as a question rather than a statement. The latency increases indicate that subjects required longer time periods to evaluate both types of stimuli and to come to a decision about them - due perhaps to an additive combination of slowed sensory processing

of the discrete auditory stimuli (supported by the visual transient data) and an overall slowing of neural processing, extending now into the parietal cortex. However, it is difficult to separate these two influences to any degree since the earlier, sensory peaks associated with the auditory transient were not evaluated for this task. Future evaluation of the auditory P300 in the evaluation of drug effects will need to take this into account.

One final issue to be considered at this point is that whereas a lower amplitude P300 can be caused by decreased confidence in one's decision, whether one is right or wrong, a higher amplitude P300 can be elicited when confidence is high, even if the response or choice is incorrect (Hillyard, Hink, Schwent, & Picton, 1973). Such occurrences in response to the tones as the error rate increased could have an effect on the variability of the individual responses and thus decrease the averaged amplitude. Since this task did not have the capability of allowing single trials to be recalled, high confidence "misses" could not be removed from these data. As a result, the averaged P300 in this task most likely contains both types of responses. However, regardless of these considerations, the highly significant differences in P300 amplitude and latency, accompanied by a significantly increased error rate, indicate a strong decrement in the cognitive performance of the subjects. Basically, subjects were not only increasing the amount of incorrectly processed auditory information, but were also taking longer to do it.

The P300 to visual information was measured in response to both the short term memory task and the spatial processing task. In contrast with

the auditory discrimination task, both of these tasks were active in terms of requiring a button press signifying the classification of the stimulus as "same" or "different." This requirement generated reaction times from the onset of the critical stimulus that could be compared to the P300 data in an effort to use the same task to compare both behavioral and cognitive performance.

In the short term memory task, the significant P300 latency increases and amplitude decreases are evidence that cognitive decrements similar to those in the auditory discrimination task were taking place. The latency increases show that the decision point took longer to reach in all levels of difficulty for both the positive and negative sets, a finding which is supported by the reaction time data. The amplitude changes generally support the arousal and confidence issues discussed previously. However, in spite of these decrements, adequate processing, as reflected by the percent correct measure was, for the most part, being maintained. Since the individual trial data were available in this task, it was found that the significant decrements in positive sets 1 and 5 were due primarily to subjects incorrectly classifying the positive set number as belonging to the negative set rather than not responding to it at all. Surprisingly, the accuracy of the response to all other positive and negative set classifications was unchanged. So it appears that diazepam's effects on short term memory are greater in terms of the process of making a decision and executing a response rather than on the accuracy of the decision. Clarke, Eccersely, Frisby and Thornton (1970), who studied the amnesiac effects of diazepam, have concluded that its effect is one of poorer acquisition of information rather than the reduction of the ability to recall that information once it

had been learned. Ghoneim and Mewaldt (1975) tested the immediate recall of eight digit number sequences one hour after diazepam injection and also found no significant decrements. These authors did find significant memory loss, however, if recall was delayed. Since our task was based on immediate rather than delayed recall our results generally agree with their findings. The nature of the P300 amplitude and latency decrements may therefore be more adequately explained by the reaction time slope and intercept decrements. As mentioned previously, the reaction time slope is interpreted as a "memory look up time" during which a stimulus is compared with other stimulus alternatives in the memory set. In other words, it can reflect the time per unit item involved in scanning the memory and retrieving information. That this variable showed significant increases for both positive and negative sets indicates that diazepam's effect on immediate recall is to increase the amount of time required to evaluate and process each number in a particular set. This cognitive delay is further supported by the slope of the P300 latency, which also shows a significant per item increase--only this time, with respect to the actual point of decision.

Similarly, the significant increases in reaction time intercepts for both positive and negative sets support not only that the time needed to execute the motor response was increased, but that the time required to encode or preprocess the stimulus into suitable form for content evaluation was also affected. This, in turn, is supported by the P300 latency intercept increases, which yielded further neurological evidence of cognitive input-output processing decrements.

In summary, the short term memory task behavioral data indicated significant diazepam induced reaction time increases that were generally unaccompanied by reductions in the accuracy of the response. The concurrently measured evoked response data provided strong evidence that the deficits were due to increases in encoding, processing, and overall input-output time. Although this is not the first time that this paradigm has been used to detect the cognitive effects of chemical exposure, it is, to our knowledge, the first time evoked response data has been measured concurrently to assess precisely where in the cognitive process the drug induced deficits occurred.

The results of the spatial processing task indicated that immediate matching to memory is affected similarly by diazepam when the information presented by the critical stimulus requires the manipulation and comparison of spatial information. It must also be noted that the short term memory task above employed what was essentially a fixed set procedure where, for the duration of any 40 number trial, the memory set remained the same. This, in a sense, allowed rehearsal of the critical numbers each time a new comparison number was presented. In contrast, the spatial processing task was a variable set procedure, where the subjects were presented with new and different target stimuli each time, with no rehearsal possibilities. This task, therefore, may be said to test even shorter term recall than the previous task. In both difficulty conditions, reaction times, as measured by the button press, were slowed significantly, while the accuracy of the response, whether requiring mental rotation or not, remained unaffected. The P300 amplitude and latency data again indicate that subjects were

taking significantly longer periods of time to reach their decision points and did so with decreased levels of activation and confidence.

There seems little doubt, looking at the P300 data in its entirety, that these data can be used as an index of cognitive performance and its decrements in tasks of varying difficulty presented in different sensory modalities. The results in terms of increased reaction times were indexed by P300 latency changes each time they occurred, whether or not accuracy was affected. The P300 amplitude changes consistently reflected diazepam-induced decrements in neural activation, due most likely to attentional decline accompanied by lowered confidence in the decisions made. Further, mathematical treatment of the reaction time and P300 latency data provided corresponding indications of the processing stages where the cognitive decrement occurred.

In summary, this experiment showed that an orally administered 10mg dose of diazepam produces large and significant effects on most of the variables considered. Physiological, behavioral, and cognitive deficits were measured in all subjects from 30 minutes to 1 hour 30 minutes postingestion. The power calculations presented in Tables 5-8 are generally very high, reflecting a high probability of being able to find a significant difference where one actually exists. The literature also indicates that differences of the magnitude obtained in the present study are substantial in terms of decrements in performance capabilities. The neurophychological test battery performed flawlessly in terms of stimulus presentation, the gathering of multi-channel EEG and EOG data, the storage of that data, and the subsequent measurement of the averaged response. The ecological

validity of the battery was improved by the inclusion of the two CTS behavioral tasks, which allowed measurement of short term memory performance and tracking abilities. The unique incorporation of evoked response measurement, linked to that performance, provided an unprecedented evaluation of the cognitive, behavioral, and perceptual effects of diazepam exposure. The calibration of the battery for drug effects is now possible. It should be clear from these data that the overall battery can be used to answer questions in both basic and applied settings. As a standardized measurement device, its contributions to the field could range from medical diagnosis to learning deficits to aircraft design and human engineering interests. It is surprising that these and other evoked response techniques which demonstrate good reliabilty, and which can consistently be related to behaviors in the laboratory, have not enjoyed a more widespread use in these disciplines, particularly in field trials designed to test the laboratory findings in the real world. It is hoped that this experiment demonstrates the versatility, sensitivity, objectivity, specificity, and emphasis on process rather than simple product that will allow these techniques to be generalized from one research or applied interest to another.

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APPENDIX A

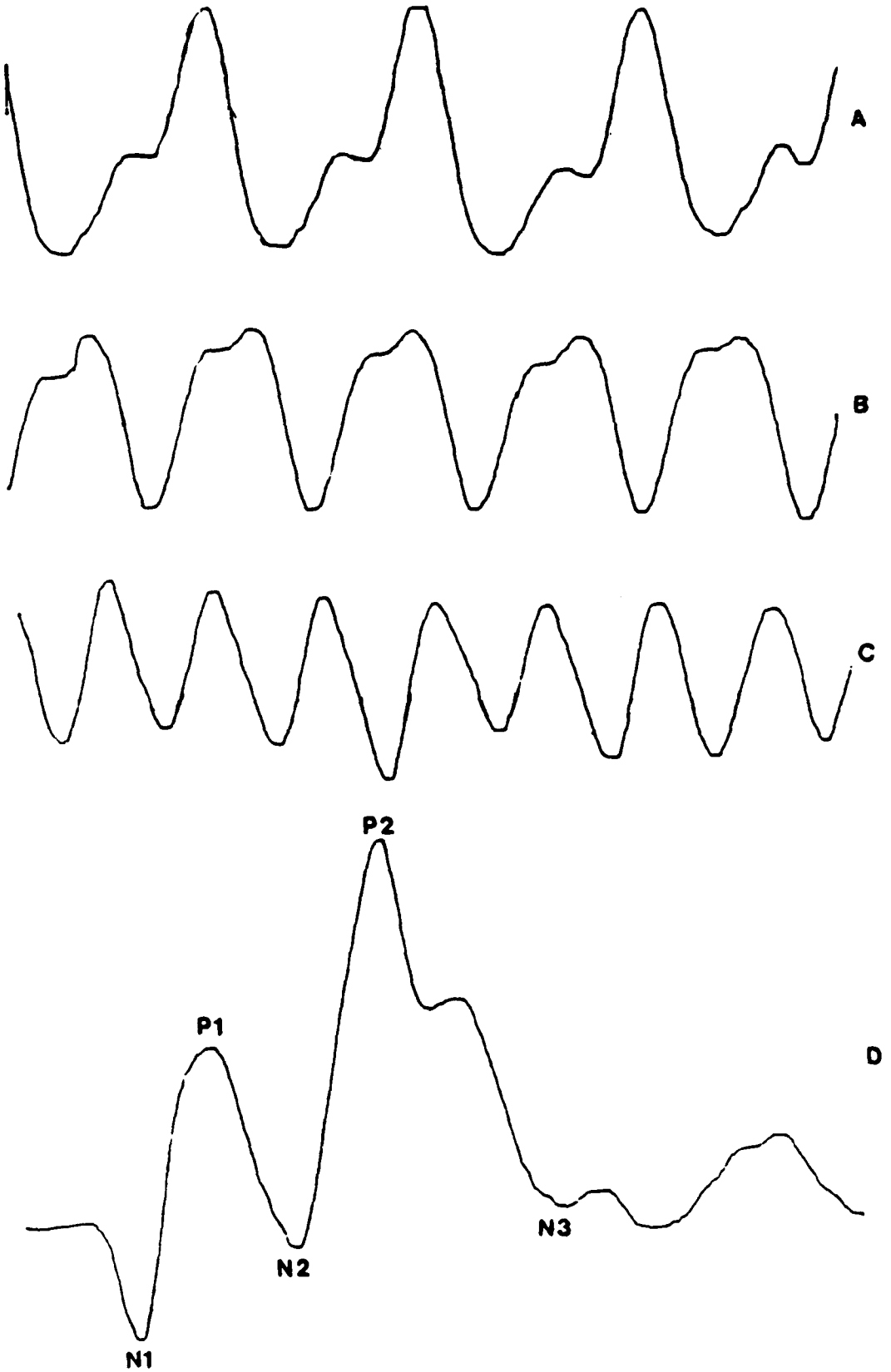
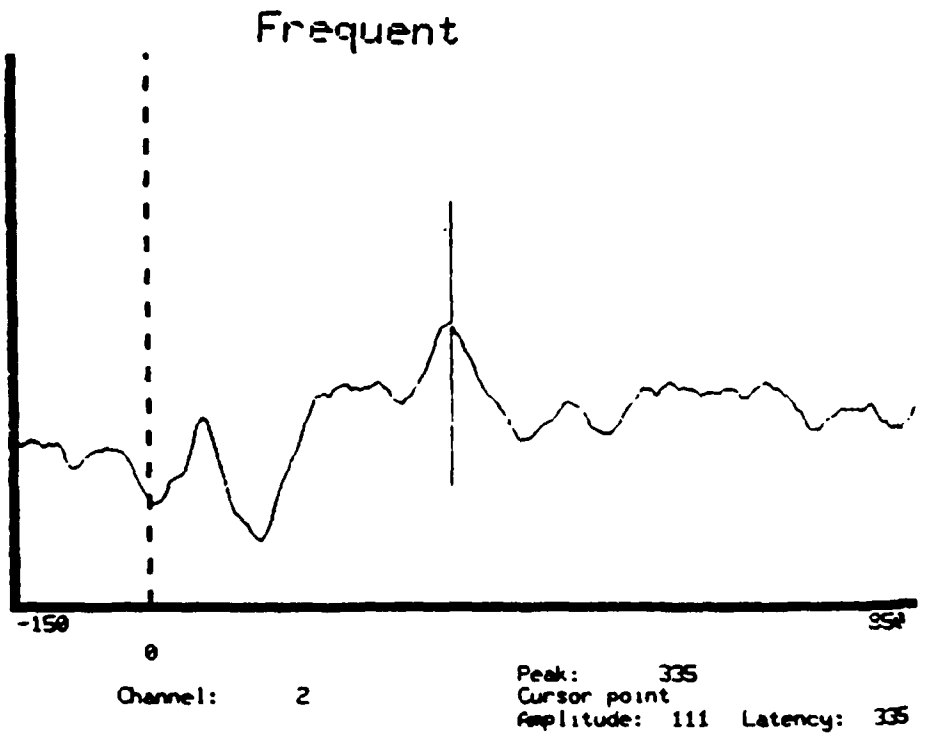


FIGURE 1. Single subject traces (subject 22) for the steady state evoked response to the patterned stimulus (A = 7.5Hz; B = 10Hz; C = 15Hz) and to the strobe transient (D).



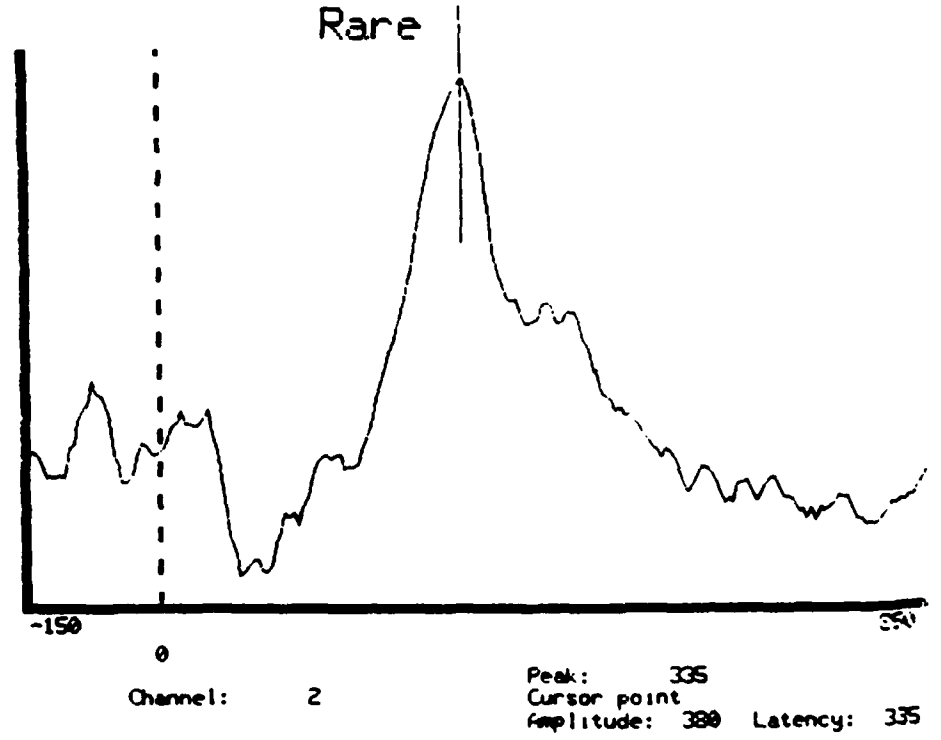
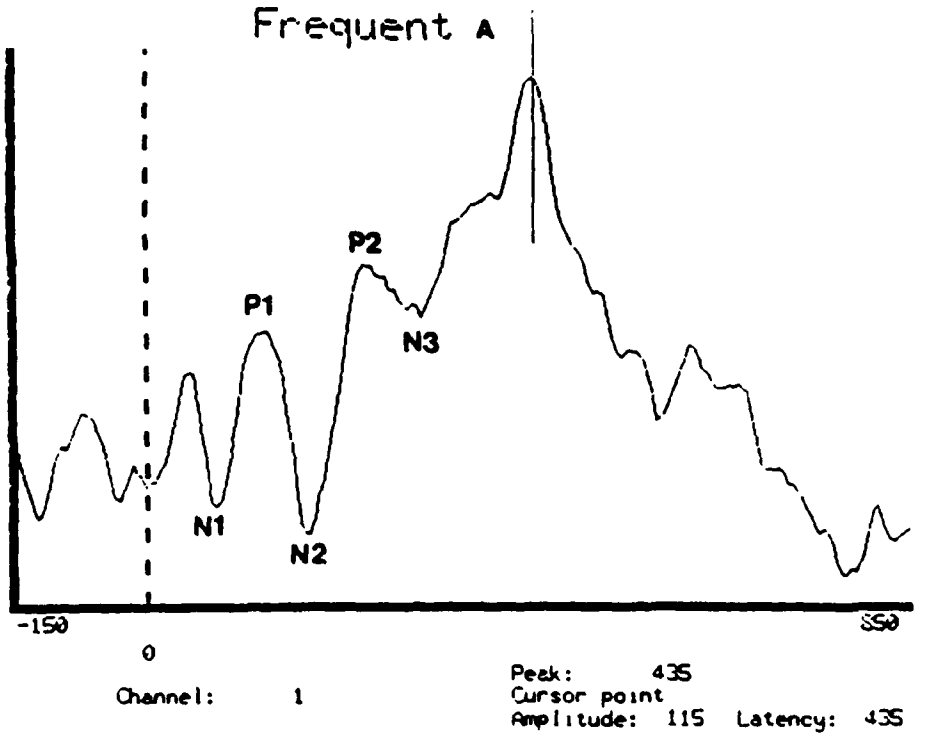


FIGURE 2. Single subject auditory evoked responses to the auditory discrimination task (subject 14). P300 is marked by the vertical line. The dotted line is the stimulus (tone) onset.



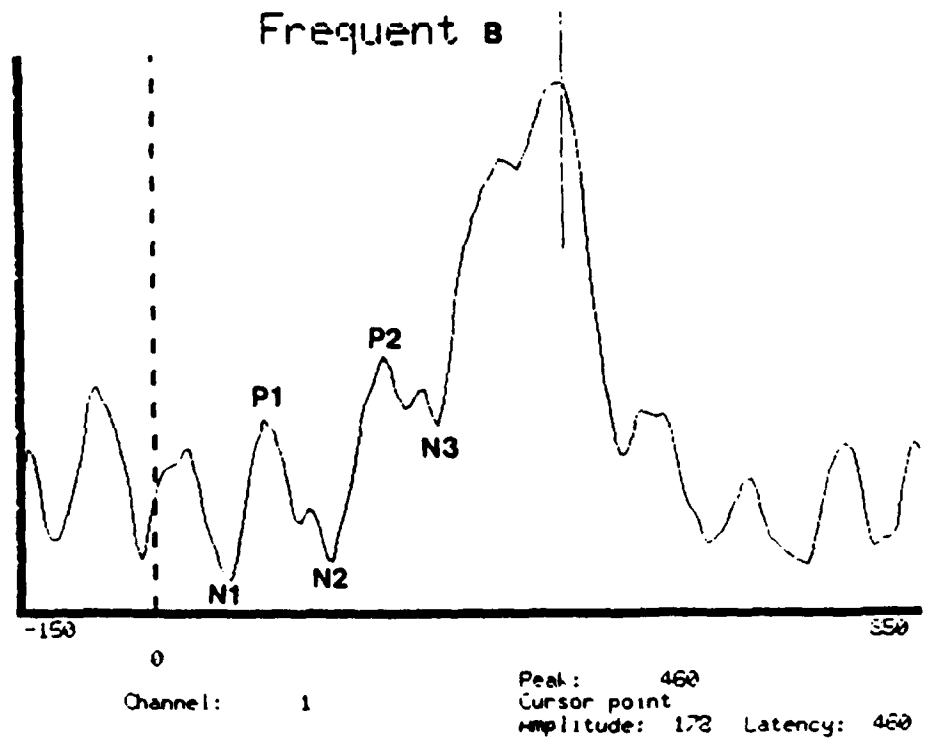


FIGURE 3. A single subject (subject 12) transient evoked response averaged during the tracking task (A = low difficulty; B = high difficulty). Large peak is in response to motor activity.

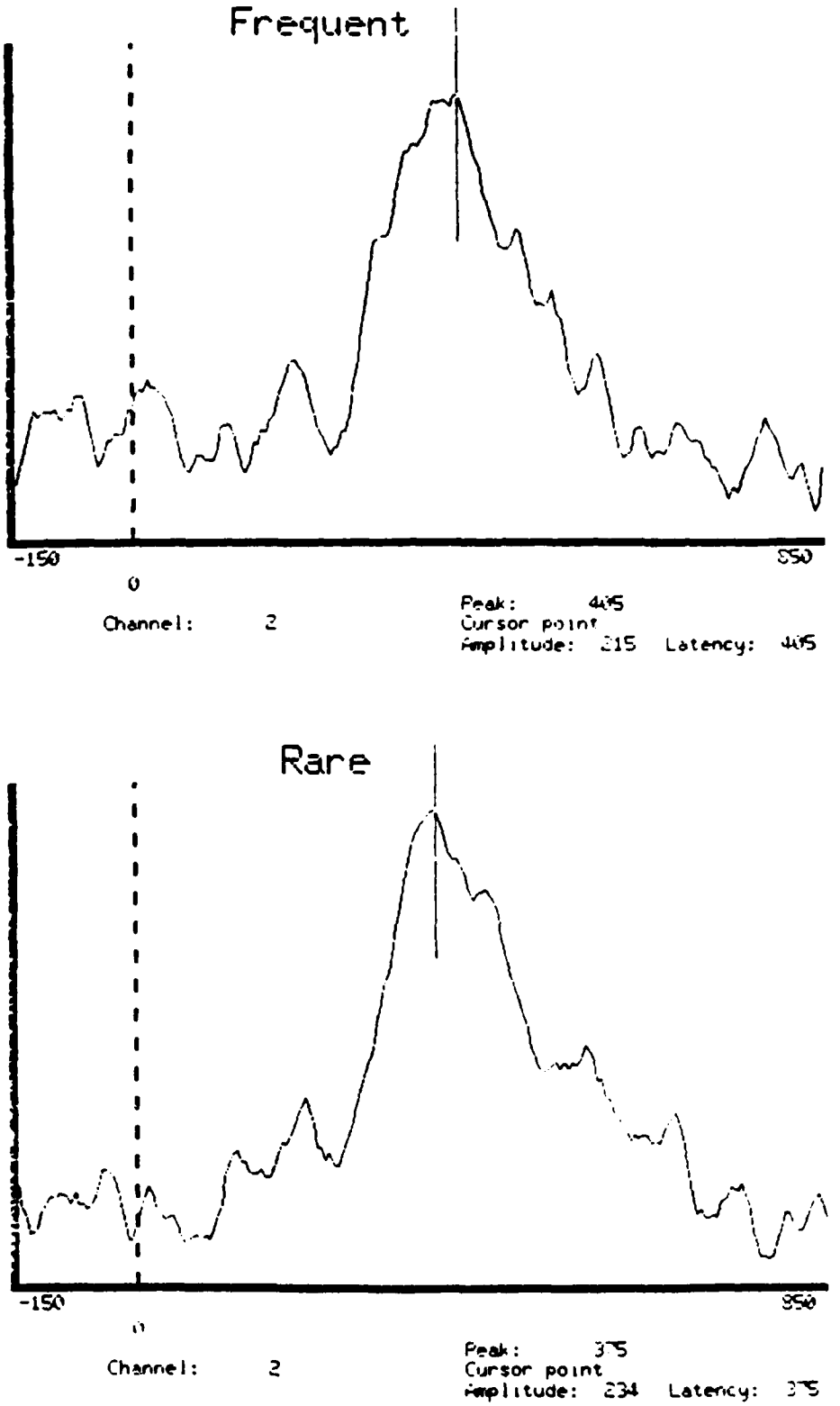
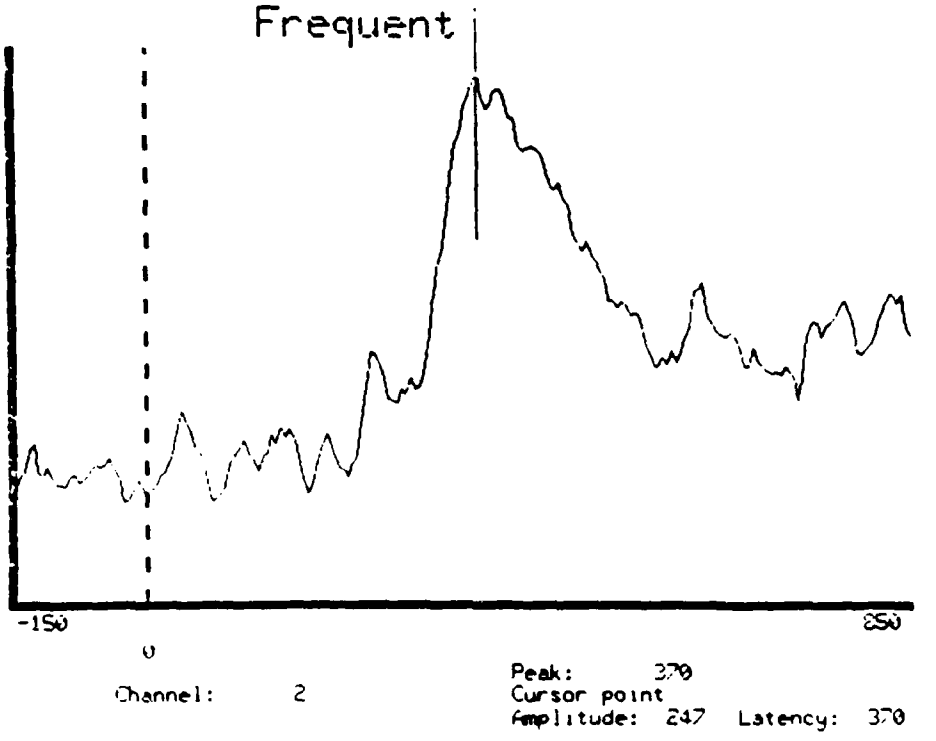


FIGURE 4. Single subject (subject 6) transient evoked response averaged during the short term memory task (frequent = nonmemorized; rare = memorized). P300 is marked by the vertical line.



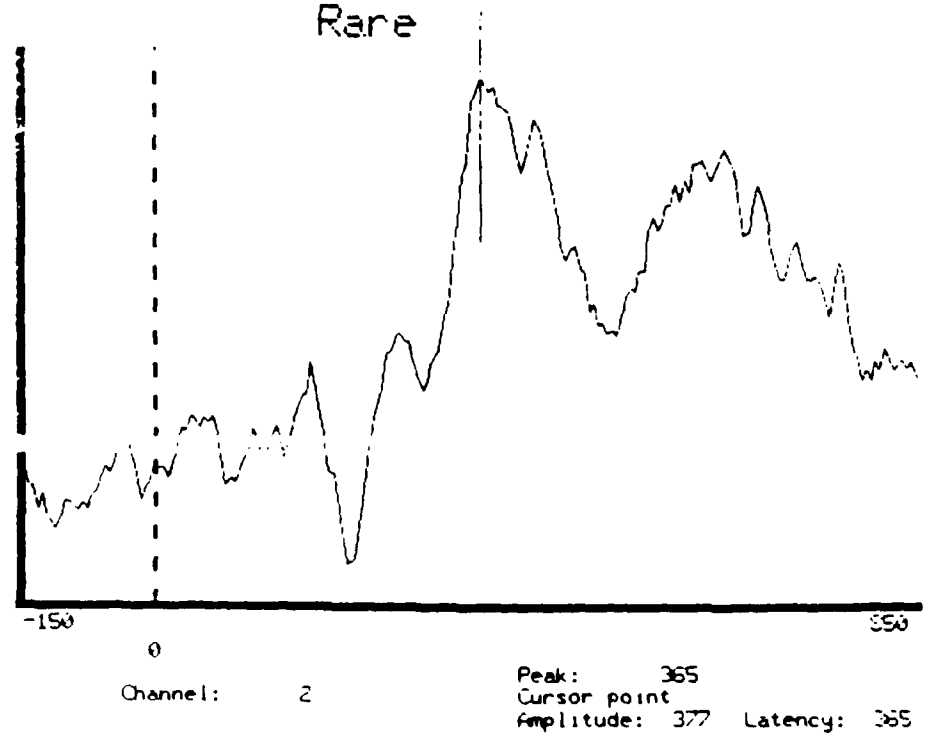


FIGURE 5. Single subject (subject 24) transient evoked response averaged during the spatial processing task (frequent = different; rare = same). P300 is marked by the vertical line.

APPENDIX B

TABLE 6

Power and related values for components of the visual tests

Measure	Frequency/ Component	Mean Difference	Standard Deviation	Noncentrality Parameter	Power
Steady State Mean Coherence	Low	- .0046	.1241	.03957	.05 *
	Med	.0738	.1949	4.0110	.49 *
	High	.0218	.08129	2.0219	.27 *
Steady State Transmission Speed (msec)	Low	-77.1	89.54	20.731	.99
	Med	-41.2	72.47	9.0382	.83
	High	-53.9	76.59	13.898	.94
Checkerboard Amplitude (uV)	7.5 Hz	1.47	1.75	19.724	.99
	10 Hz	1.08	1.74	10.755	.86
	15 Hz	.61	1.80	5.790	.64
Checkerboard Latency (msec)	7.5 Hz	-9.0	11.91	16.082	.97
	10 Hz	-8.31	17.52	6.2980	.68
	15 Hz	-6.09	11.10	8.4402	.80
Strobe Amplitude (uV)	N1, P1	1.52	2.35	11.746	.91
	P1, N2	1.96	3.04	11.662	.91
	N2, P2	2.54	2.83	22.527	.99
	P2, N3	2.32	2.24	29.971	.99
Strobe Latency (msec)	N1	-8.37	16.44	7.2725	.74
	P1	-12.37	14.41	20.669	.99
	N2	-13.97	15.75	21.964	.99
	P2	-18.50	20.98	21.669	.99
	N3	-20.63	25.53	18.267	.98
CFF (Hz)	Cycles per second	-.243	2.25	.3301	.09*

Note. (*) Indicates that the variable was not significantly affected by diazepam
(-) Indicates an increase in the variable (+) Indicates a decrease

TABLE 7

Power and related values for components of the auditory discrimination task

Measure	% Correct/ Tone Set	Mean Difference	Standard Deviation	Noncentrality Parameter	Power
P300 Amplitude (uV)	Rare Tone	3.64	5.12	14.176	.95
	Frequent Tone	1.40	2.24	10.971	.89
P300 Latency (msec)	Rare Tone	-62.9	31.16	114.16	1.0
	Frequent Tone	-81.1	60.75	49.93	.99
Per Cent Correct	%	9.93	13.66	14.797	.96

Note. (+) Reflects a decrease
(-) Reflects an increase

TABLE 8

Power and related values for components of the unstable tracking task

Measure	Condition/ Component	Mean Difference	Standard Deviation	Noncentrality Parameter	Power
Tracking Error	Low	- 7.91	10.44	16.050	.97
	High	- 7.39	10.40	14.158	.95
Edge Violations	Low	- 3.12	5.51	8.9760	.82
	High	-17.54	29.56	9.8502	.86
Amplitude (Low Difficulty) (uV)	N1, P1	.383	1.63	1.5389	.22 *
	P1, N2	1.09	1.66	11.952	.92
	N2, P2	1.85	2.22	19.334	.99
	P2, N3	.92	2.16	5.0889	.59
Latency (Low Difficulty) (msec)	N1	-29.47	32.12	23.47	.99
	P1	-39.27	32.17	41.632	.99
	N2	-40.10	39.80	31.392	.99
	P2	-49.60	34.01	59.536	1.0
	N3	-51.60	43.20	39.952	.99
Amplitude (High Difficulty) (uV)	N1, P1	.28	5.29	.0654	.06 *
	P1, N2	1.05	3.54	2.4606	.33 *
	N2, P2	1.18	3.26	3.6734	.46 *
	P2, N3	.66	2.67	1.7160	.24 *
Latency (High Difficulty) (msec)	N1	-25.8	43.35	9.8973	.86
	P1	-28.6	43.39	12.250	.92
	N2	-27.8	43.86	11.248	.90
	P2	-38.0	36.90	29.743	.99
	N3	-38.7	45.04	20.701	.99

Note. (*) Indicates that the variable was not significantly affected by the diazepam
(+) Reflects a decrease (-) Reflects an increase

TABLE 9

Power and related values for components of the short term memory task

Measure	Memory Set	Mean Difference	Standard Deviation	Noncentrality Parameter	Power
Reaction Time (msec)	Positive Set 1	- 58.6	79.44	10.917	.89
	Positive Set 3	- 88.6	120.62	15.073	.96
	Positive Set 5	-153.6	173.97	21.833	.99
	Negative Set 1	- 52.6	97.87	8.0871	.78
	Negative Set 3	-111.4	144.53	16.628	.98
	Negative Set 5	-124.6	128.52	27.152	.99
Per cent correct	Positive Set 1	3.45	5.75	10.079	.86
	Positive Set 3	2.02	7.23	2.1912	.30 *
	Positive Set 5	5.89	10.97	8.0849	.78
	Negative Set 1	.897	3.75	1.5841	.23 *
	Negative Set 3	1.37	7.03	1.0625	.17 *
	Negative Set 5	2.62	7.03	3.8824	.47 *
P300 Amplitude (uV)	Positive Set 1	2.44	3.63	12.675	.93
	Positive Set 3	1.71	2.87	9.9292	.86
	Positive Set 5	1.04	2.78	3.9264	.48 *
	Negative Set 1	1.53	2.03	15.990	.97
	Negative Set 3	2.06	2.67	16.615	.98
	Negative Set 5	1.48	2.44	10.265	.87
P300 Latency (msec)	Positive Set 1	-64.9	39.65	75.111	1.0
	Positive Set 3	-83.5	42.01	110.38	1.0
	Positive Set 5	-72.6	30.15	162.31	1.0
	Negative Set 1	-58.1	31.20	97.105	1.0
	Negative Set 3	-59.2	44.44	49.645	.99
	Negative Set 5	-82.9	59.80	53.910	1.0
Reaction Time Slope	Positive Sets	-18.3	33.54	8.3364	.79
	Negative Sets	-23.6	29.28	18.185	.98

TABLE 9 (Continued)

Measure	Memory Set	Mean Difference	Standard Deviation	Noncentrality Parameter	Power
Reaction Time Intercept	Positive Sets	- 49.1	86.19	9.012	.83
	Negative Sets	- 46.5	105.85	5.4162	.61
P300 Latency Slope	Positive Sets	- 3.04	7.13	5.0889	.59
	Negative Sets	- 5.75	11.57	6.9189	.72
P300 Latency Intercept	Positive Sets	- 67.9	49.72	52.229	1.0
	Negative Sets	- 48.1	47.76	28.363	.99

Note. (*) Indicates that the variable was not affected by the diazepam
(+) Reflects a decrease (-) Reflects an increase

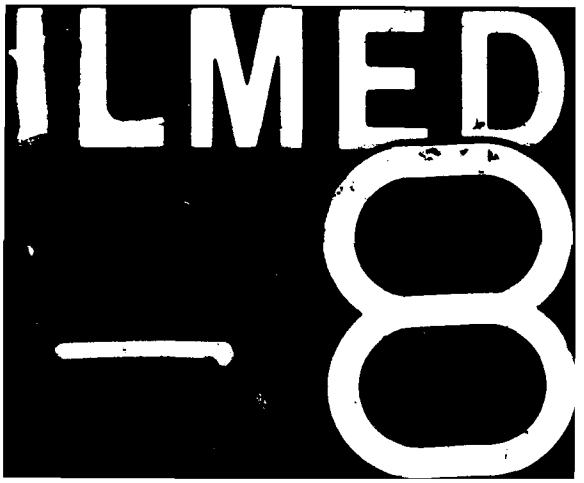
TABLE 10
Power and related values for components of the spatial processing task

Measure	Difficulty Condition/ Component	Mean Difference	Standard Deviation	Noncentrality Parameter	Power	
Per cent Correct	Low	1.61	6.81	1.5652	.23	*
	High	- 1.54	5.85	2.4835	.33	*
Reaction Time (msec)	Low	-94.07	94.02	28.069	.99	
	High	-134.93	231.9	9.4350	.84	
P300 Amplitude (uV)	Low (same)	2.64	4.14	11.413	.90	
	High (same)	1.16	2.76	4.9628	.57	
	Low (diff)	2.41	3.03	17.691	.98	
	High (diff)	2.05	2.52	18.527	.99	
P300 Latency (msec)	Low (same)	- 66.63	44.93	61.651	1.0	
	High (same)	- 72.37	56.04	46.628	.99	
	Low (diff)	- 69.90	52.95	48.762	.99	
	High (diff)	- 65.17	38.49	80.299	1.0	

Note. (*) Indicates that the variable was not affected by the diazepam
(-) Indicates an increase in the variable (+) Reflects a decrease

APPENDIX C

When subjects failed to respond to the stimulus number in the short term memory task, one of several results was possible. Several subjects realized that they had missed responding to the previous number and responded to the new stimulus number. This resulted in a zero value for reaction time to the missed number and a normal reaction time to the number following it on the printed output. On other similar occasions, subjects responded to the missed number in haste while the new number was on the screen. This resulted in a zero value for reaction time to the missed number and an abnormally short reaction time to the following number. On still other occasions, subjects continued to process the missed number while the new number was on the screen, realized the new number was there, and responded with the button press only after processing the new number. This resulted in a zero value for reaction time to the missed number and an abnormally long reaction time to the number following it. These situations required the establishment of a rejection criterion to be used to remove all the obvious outlying reaction times from the analysis. Since the standard deviation of the reaction times was readily available, it was decided to delete any reaction time that differed from the computed mean by ± 2 standard deviations. To accomplish this, each set of response printouts was inspected, the appropriate reactions times were deleted, and the mean reaction time was recomputed by hand for positive and negative sets.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